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Inheritance of resistance to oedema disease in the pig: Experiments with an *Escherichia coli* strain expressing fimbriae 107

H.U. Bertschinger*, M. Stamm* and P. Vögeli*

*Institute of Veterinary Bacteriology, University of Zürich, Zürich, Switzerland

bInstitute of Animal Production, Federal Technical University, ETH-Zentrum, Zürich, Switzerland

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**ABSTRACT**

Inheritance of resistance to intestinal colonization with *E. coli* causing oedema disease is hypothesized to be under the control of one locus consisting of two alleles with susceptibility (S) dominating resistance (s). This mode of inheritance was investigated by mating pigs, resistant and susceptible to the disease, and examining the offspring. Weaned piglets were repeatedly inoculated orally with $5 \times 10^5$ CFU per pig per day of a streptomycin resistant strain of *E. coli* serotype O139:K12(B):H1:F(107) and susceptibility determined by daily semiquantitative cultural examination of rectal swabs. Using results obtained from offspring, 5 boars were retrospectively assigned the genotype ss, 1 was assigned Ss, and 2 were assigned SS. Nine sows were designated ss, 8 classified Ss and 4 SS. Ninety two pigs resulted from matings regarded as ssxss; 89 (97%) of these were resistant to colonization and oedema disease. Of the 168 pigs from Ssxss matings, 83 (49%) were resistant, while only 13 (9%) of 146 pigs from matings with at least one SS parent were classified resistant. The results are compatible with inheritance being controlled by one locus and with susceptibility dominating resistance to oedema disease.

**INTRODUCTION**

Oedema disease of pigs is an enterotoxaemia characterized by generalized vascular damage. The latter is caused by a toxin, Shiga-like toxin-II variant (SLT-IIv), produced by certain strains of *E. coli*. It occurs widely throughout the world, although incidence changes with time and geographic location (Bertschinger and Nielsen, 1992). In Switzerland, the disease is an important cause of death in weaned pigs. Variable morbidity has been observed within
and between individual litters in natural outbreaks (Luke and Gordon, 1950; Timoney, 1950) as well as under experimental conditions (Smith and Halls, 1968; Bertschinger et al., 1986). However, variable morbidity is not due to inherent resistance to parenterally administered toxin (MacLeod et al., 1991). Smith and Halls (1968), and Bertschinger et al. (1986) reported that resistance to oedema disease is associated with absence of intestinal colonization after oral administration of bacterial cultures. An E. coli strain causing oedema disease colonized the small intestine in a manner similar to enterotoxigenic E. coli (Methiyapun et al., 1984). In contrast, in pigs experimentally infected with E. coli of human origin producing other types of Shiga-like toxins, colonization occurs in the large intestine and is associated with characteristic changes of enterocytes called “attaching and effacing” lesion (Tzipori et al., 1987).

Sellwood et al. (1974) investigated the adherence in vitro of enterotoxigenic E. coli with fimbriae F4 to enterocyte brush borders. They detected that a significant proportion of pigs yielded brush border preparations to which E. coli with fimbriae F4 did not adhere. They suggested that adherence/non-adherence is genetically controlled by two alleles, and that adherence is dominant over non-adherence. Later work by the same group and by other workers confirmed these findings. Oral inoculation of weaned pigs of the adhesive phenotype with E. coli bearing fimbriae F4 results in severe diarrhoea, whereas pigs of the non adhesive phenotype develop no clinical signs and do not excrete the challenge strain (Rutter et al., 1975; Sarmiento et al., 1988). However, suckling piglets with the adhesive phenotype may seem to be resistant to infection, if they receive protective antibodies with the sow's milk (Rutter et al., 1975, Sellwood, 1979). Further evidence that adherence and non-adherence may be genetically determined is provided by the finding that fimbriae F4 exist as 3 antigenic variants ab, ac and ad, and in brush-border adhesion tests, each variant binds to a distinct, specific receptor; receptors for each variant are inherited independently (Bijlsma et al., 1982; Rapacz and Hasler-Rapacz, 1986). Phenotypic resistance of piglets to in vitro adhesion has also been observed with fimbriae F5; however, it is not known if the resistance is of genetic nature (Seignole et al., 1991).

In a previous study, we investigated factors affecting the susceptibility of weaned pigs to oedema disease by inoculating pigs with a pathogenic strain of E. coli. The boar was found to represent the most significant source of variability (Bertschinger et al., 1986). This boar effect suggested an underlying genetic determinant for susceptibility. To investigate this “boar effect” pigs, both resistant and susceptible to colonization, were mated and the offspring analysed for the degree of susceptibility to colonization. The mode of inheritance observed suggests that resistance to colonization with E. coli bearing fimbriae 107 is inherited as a single recessive trait.
MATERIALS AND METHODS

**Pigs**
An experimental herd was built up at the Institute of Veterinary Bacteriology with boars and sows originating from a pedigree SPF Improved Landrace herd. The pigs born in the experimental herd were individually tattooed before weaning, and weaned pigs were immediately removed from the premises.

**Bacteria and media**
The colonization tests reported were performed with *E. coli* strain 124/76 of serotype O139:K12(B):H1:F(107) (Bertschinger et al., 1990). Inocula were grown aerobically in Trypticase Soy broth (BBL Microbiology Systems, Cockeysville, MD) at 37°C for about 20 h. Blood agar was made from Trypticase Soy agar (BBL) with 5% sheep blood. Streptomycin 400 μg/ml was added to allow reisolation of the inoculated bacteria from faecal material.

**Colonization test**
Immediately after weaning at an average age of 28 (21 to 42) days individual pigs were placed for a period of 2 weeks in disinfected wire mesh cages. The cages were equipped with fully perforated plastic floors, feeding bowls, and drinking nipples. They were placed in ventilated isolation rooms at a temperature of 26°C (±1°C). Pigs were fed a commercial type compound feed for suckling and weaned pigs. The feed was devoid of antimicrobial additives and organic acids. It contained 19% crude protein, 17% digestible protein (pig), 3% crude fibre, 3% fat, and 13 MJ/kg digestible energy (calculated contents).

Pigs were inoculated on days 4, 6, 8, 10 and 12 after weaning with the bacteria by thoroughly mixing 20 ml of inoculum with 250 g of dry feed. The inoculum was prepared by diluting the 20 h broth culture 1:10000 in sterile demineralized water. The viable count in the feed was $2 \times 10^3$ CFU/g, and the total daily dose $5 \times 10^5$ CFU per pig. Inoculum was not given to pigs which showed a faecal *E. coli* score of 3 or more on a scale described below.

Faecal shedding of the bacteria was monitored by daily rectal swabbing with cotton swabs on wooden applicator sticks. The faecal material was suspended in 1.5 ml of Trypticase Soy broth, homogenized by vortexing (Vortex Génie, Auer, Bittmann, Soulié, CH 8953 Dietikon), and one loopful spread on a blood agar plate with streptomycin. After incubation for 9 to 22 h the numbers of characteristic haemolytic colonies were estimated and given a score from 0 to 8. The scores were determined by comparison with a standard of plates inoculated with tenfold dilutions of a broth culture. Reproducibility was poor with dense growth, therefore a dilution of 1:1000 of the faecal suspension was prepared and plated the same way whenever a score of 4 or more was to be expected. Viable counts performed in parallel from 196 samples
showed that a score of 2 corresponds to a count of 5.3 lg CFU/g of wet faeces, a score of 3 to 6.3 lg CFU, and so on.

The extent of colonization was calculated as the mean of the two highest faecal scores. Pigs with a mean peak score of 3.5, corresponding to 6.7 lg CFU/g or more, were considered susceptible to colonization. This limit was based on a lack of mortality below this value, and on scores obtained from completely resistant litters.

Abundantly colonized pigs were treated with an antimicrobial for humane reasons and also to save them for breeding. Treatment was started when a score of 5 persisted for 24 h or more. It consisted of intramuscular injection of amoxycillin (Clamoxyl, Beecham, Animal Health, Brentford, UK) at 30 mg/kg of bodyweight or of enrofloxacin (Baytril, Bayer, Leverkusen, D) at 2.5 mg/kg. Injections were given on 3 consecutive days.

Plating of the faecal suspensions on plain blood agar was done to rule out spontaneous infections with other strains of *E. coli* pathogenic for weaned pigs. Rectal swabs were taken 9 and 2 days before weaning, at the time of weaning, and 2 days thereafter. Haemolytic coliform colonies on plain blood agar were checked for identity with the inoculum by parallel subculture on blood agar with and without streptomycin. After completion of the experiment, the pigs were examined bacteriologically for, at least, a further two weeks.

**Estimation of genotypes**

Genotypes of pigs were estimated in order to test the hypothesis that susceptibility and resistance to colonization would be controlled by two alleles, and that susceptibility would be dominant over resistance. The genotypes of boars and sows were estimated based on their own colonization scores, and on results of progeny originating from at least one mating with a resistant partner. They were classified as resistant (ss) if there were no susceptible pigs in that litter, heterozygously susceptible (Ss) if up to 50% of weanlings were susceptible, and homozygously susceptible (SS), if between 50 and 100% of the progeny were susceptible. Genotypes of some parents were derived from colonization tests using deviating doses of culture and application schemes for inoculation (data not shown).

RESULTS

The majority of the newly weaned pigs suffered for at least one day from diarrhoea; but this was not related to colonization with the inoculated bacterial strain. The faecal scores for the shedding of the inoculated strain rose but this was slower compared with colonization of newborn pigs with enterotoxigenic *E. coli* (Fig. 1). In some pigs, the increase of the faecal scores was delayed until close to the end or, exceptionally, beyond the period of housing in
INHERITANCE OF RESISTANCE TO OEDEMA DISEASE

E. coli score

Days after 1st Inoculation

Fig. 1. Three typical examples of the course of the daily faecal scores of the inoculated *E. coli*. No. 8067 = susceptible treated pig. No. 8046 = susceptible pig without treatment. No. 8060 = resistant pig. † = inoculation. ▲ = treatment with amoxycillin.

TABLE 1

Antimicrobial treatment and mortality due to oedema disease in 406 weaned pigs inoculated via feed with *E. coli* strain 124/76

| Genotypes of parents | Numbers of pigs | Treated with antimicrobial | Dead or killed |
|----------------------|-----------------|----------------------------|----------------|
|                      | Tested          |                            |                |
| ss × ss              | 92              | 0                          | 0              |
| Ss × ss              | 168             | 47 (28.0%)                 | 4 (2.4%)       |
| SS × ss              | 146             | 100 (68.5%)                | 11 (7.5%)      |

1 Genetic classification based on own results and on results of progeny.
2 Treatment with amoxycillin or enrofloxacin was started when a faecal score of 5 persisted for at least 24 h.
3 Oedema disease diagnosed at post mortem examination.
Fig. 2. Intervals between start of inoculation and attainment of a faecal shedding score of 5 with the 167 pigs reaching this score.

| Genotypes of boars | Numbers of litters and pigs weaned from sows of genotypes |
|--------------------|-----------------------------------------------|
|                    | ss (n=9)                                      | Ss (n=8)                                      | SS (n=4)                                      |
|                    | Litters | Pigs | Litters | Pigs | Litters | Pigs |
| ss (n=5)           | 12      | 92   | 19      | 159  | 3       | 31   |
| Ss (n=1)           | 1       | 9    | 0       | 0    | 0       | 0    |
| SS (n=2)           | 4       | 35   | 7       | 52   | 4       | 28   |

1Estimation of genotypes of parents was based on own colonization test results and on results from progeny, which are not shown completely.

| Genotypes of parents | Number tested | Resistant pigs |
|----------------------|---------------|----------------|
|                      | Litters | Pigs | Observed | Expected |
| ss×ss               | 12      | 92   | 89 (97%) | 92 (100%) |
| Ss×ss               | 20      | 168  | 83 (49%) | 84 (50%)  |
| SS×ss               | 18      | 146  | 13 (9%)  | 0 (0%)    |

1Genotypic classification based on own colonization test results and on results from progeny.
2Pigs with faecal shedding scores ≤3.4 were considered resistant.
Fig. 3. Relative frequencies of mean peak faecal shedding scores of the 406 pigs originating from ss × ss, Ss × ss, and SS × all genotype matings. Faecal scores for shedding of the orally inoculated $E. coli$ strain were determined by daily cultural examination of faecal swabs. The mean was calculated from the two highest scores observed with each pig.

Individual cages (Fig. 2). Antimicrobial treatment had to be given to 147 pigs (Table 1). Fifteen pigs died or were killed with advanced signs of oedema disease. Four of these were found dead before treatment could be started, and most of the others died or were killed before the second injection. Both amoxicillin and enrofloxacin led to a rapid fall of the $E. coli$ scores below the level of detection (Fig. 1). In many pigs, the scores rose again after termination of treatment, and some pigs needed a further course of treatment. Infections by other strains of pathogenic $E. coli$ occurred rarely and each time shortly before termination of the test period.

Of the boars used in the experiment, 5 were classified as genotype ss, 1 was classified Ss, and 2 classified SS (Table 2). Nine of the sows used were classified ss, 8 were classified Ss, and 4 classified SS. From 50 matings a total of 406 pigs were weaned. Two pigs died after weaning from causes not related
to the experiment and so are not included in this figure or shown in the tables. Ninety two pigs were born after ss×ss matings, of which 89 (97%) were resistant to colonization (Table 3). Of 168 pigs resulting from Ss×ss matings 83 (49%) were found to be resistant. Of the 146 pigs originating from matings with at least one SS parent, 13 (9%) were classified resistant. The frequency histogram of the mean peak shedding scores shows some overlap between descendants from matings of different genotypes (Fig. 3).

No antimicrobial treatments were necessary, and no deaths occurred with the progeny of ss×ss parents (Table 1). Mortality in Ss×ss litters was lower than in litters from SS×.. matings.

DISCUSSION

The outcome of this experiment confirms the existence of genetic resistance against colonization with *E. coli* bearing fimbriae 107. The segregation observed in litters originating from Ss×ss matings is compatible with one genetical locus with the two alleles S and s. S codes for susceptibility to colonization and is dominant over s, which codes for resistance. Thus only ss pigs are resistant to colonization. An identical mode of inheritance has been detected for resistance to colonization by enterotoxigenic *E. coli* bearing fimbriae F4 by Sellwood et al. (1974), and confirmed by Gibbons et al. (1977), Rapacz and Hasler-Rapacz (1986), and Bijlsma and Bouw (1987). Glycoprotein receptors in the brush border membrane were shown to be responsible for the differences between adhesive and nonadhesive phenotypes (Erickson et al., 1992).

The colonization test used allowed discrimination between susceptible and resistant pigs in a satisfactory percentage of the pigs tested. No pig classified resistant to colonization had to be treated or was affected by oedema disease. On the other hand, a significant proportion of the pigs classified susceptible had to be treated with antimicrobials. Some were so severely affected that they died or had to be killed. This finding emphasizes the reliability of the colonization test. The actual numbers of resistant and susceptible pigs found did not perfectly agree with numbers expected according to Mendelian genetics. Mean faecal scores of resistant and susceptible pigs exhibited considerable overlap, the semiquantitative technique applied to bacterial enumeration may account for some deviation. Furthermore faecal numbers of *E. coli* may be affected by a multiplicity of factors. Gastric acidity, small intestinal stasis, concentration of bacteria entering the large intestine by fluid absorption, and bacterial proliferation may increase the viable counts with resistant pigs (Smith and Halls, 1968; Sarmiento et al., 1988). Bacterial colonization of the small intestine of susceptible pigs may be affected by factors reducing the density of bacterial receptors, such as viral infection (Cox et al., 1988), or factors slowing down bacterial proliferation such as lack of nutrients or
antimicrobial substances produced by the bacterial flora of the upper gastrointestional tract (Axelsson et al., 1989). However, although satisfactory results were obtained, the test used in this pilot study is much too laborious and expensive to be applied on a larger scale for selection of resistant pigs. Searches are underway for appropriate genetic markers as well as for in vitro methods to determine intestinal receptors for fimbriae 107.

The frequency of the gene encoding resistance was higher in the experimental herd than in the herd, from where the pigs were originally obtained because selection of resistant breeders had been started at an earlier time. It cannot be decided at present, to which extent genetic resistance to oedema disease is responsible for the variation of the morbidity frequently seen in the field.

The numbers of the pathogenic *E. coli* strain in the rectal contents rose quite slowly. This contrasts with colonization of the small intestine by enterotoxigenic strains of *E. coli* in neonatal pigs, where this period may be less than half a day (Bertschinger et al., 1972). Smith and Halls (1968) inoculated weaned pigs with $10^{10}$ CFU of a strain of serotype O141:K85a,c with unknown adhesin. It was not until 3 days after inoculation that very large numbers of the inoculated strain were found in the more anterior regions of the small intestine, and that peak viable counts were attained in rectal contents. These observations suggest that the slow rise of the faecal scores in the present experiment was not due to the low number of bacteria inoculated. We have no explanation for this phenomenon and for the great variability of the intervals between the start of inoculation and peak faecal scores.

Fimbriae identical with or closely related to fimbriae 107 are quite common with *E. coli* strains causing oedema disease and/or diarrhoea in weaned pigs (Imberechts et al., 1990, Stamm et al., 1990). Breeding resistant pigs is an attractive method for prevention of diseases, for which an effective prophylaxis is not available. The feasibility of this approach will depend on the prevalence of the gene(s) encoding resistance in the pig population, improved methods for the detection of resistant pigs, and absence of negative genetic traits co-selected with this resistance (Walters and Sellwood, 1982).

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of cats used to study the efficacy of a candidate FIP vaccine demonstrated a statistically significant association (under certain challenge conditions) between the ability of a cat's serum to mediate enhancement of FIPV infectivity in vitro and the development of accelerated FIP in vivo (Olsen and Scott, 1992).

DIAGNOSIS OF FIP

It is very difficult to make a definitive diagnosis of FIP. Biopsy and subsequent histopathologic examination is the only absolutely conclusive method for antemortem diagnosis (Barlough and Scott, 1988). Short of this, a variety of factors must be taken together to support a diagnosis of FIP (Barlough and Scott, 1988; Pedersen, 1983b; Scott, 1989; Stoddart and Gaskell, 1985; Sparkes, et al., 1991). Clinicopathologically, patients may demonstrate any of the following, depending upon the particular organ system affected: elevated serum liver enzyme and bilirubin levels, elevated serum urea nitrogen and creatinine levels, elevated fibrinogen levels, decreased packed cell volumes, neutrophilia, lymphopenia, or proteinuria. Analysis of blood protein levels may be very helpful. While albumin levels may be normal or decreased, globulin levels are often increased. Serum protein electrophoresis commonly demonstrates a polyclonal gammopathy. In cases of effusive FIP, analysis of fluid obtained by abdomino- or thoracocentesis may be helpful. The fluid is generally yellow (though there may be various degrees of blood-tinging) and viscous with visible strands of fibrin. Fluid analysis should reveal a high specific gravity and elevated protein level, with variable numbers of inflammatory cells. The fluid may clot upon standing. Cerebrospinal fluid may reveal elevated protein levels and increased cellularity when FIP affects the CNS.

The ability to utilize serologic testing in the diagnosis of FIPV infection and clinical FIP is limited. An early serologic study revealed that 20% of a local general cat population and 87% of cats in FIP "problem catteries" were seropositive, but very few of the cats developed clinical disease (Pedersen, 1976b). These results suggested that there was a mild primary form of the disease (Pedersen, 1976b) and that more severe, classical FIP was an uncommon secondary sequela (Pedersen, 1983b). Subsequent to the discovery of the antigenically-related FECVs, it has been suggested that the vast majority of seropositive test results may indicate exposure to FECVs rather than FIPVs (Pedersen, 1983b). At this point, "the presence of serum coronavirus antibody in any cat, whether healthy or diseased, is indicative only of prior exposure to a coronavirus in the FIPV antigenic group" (Barlough and Scott, 1988), and has "little predictive or diagnostic value" (Scott, 1989). In addition, not all cats with FIP will have elevated coronavirus Ab titers. In a recent study, 10 of 39 cats with FIP had coronavirus titers of <= 80, and 2 of the 10 cats tested negative for coronavirus Ab (Sparkes, et al., 1991). Early