

In the Spotlight

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Endometritis in cattle: pathogenesis, consequences for fertility, diagnosis and therapeutic recommendations

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Introduction

After parturition, bacteria from the animal's environment contaminate the uterine lumen of most cattle. Infection persists in the uterus of many animals for more than three weeks, with about 15% of dairy cattle having signs of clinical endometritis. These animals have lower conception rates, take longer to conceive and are more likely to be culled for infertility than unaffected animals. So, endometritis is an expensive condition for vets and farmers to manage, rivalling the cost of other endemic diseases such as mastitis. The aim of this article is to summarise how uterine disease develops, and how to approach the diagnosis and treatment of endometritis.

Background

During and after parturition, bacteria often ascend the vagina, pass through the cervix and contaminate the uterine lumen of dairy and beef cattle. Intensively managed herds of dairy cattle often have uterine bacterial contamination rates of 90 to 100% within the first two weeks post partum. However, many of these bacteria are opportunistic contaminants and only about a third of animals will show signs of uterine infection, called metritis. Metritis is

characterised by purulent material in the uterine lumen, often with signs of systemic disease, such as pyrexia. Most bacteria are eliminated from the uterus during the first three weeks after parturition by the physical contraction of the uterus (involution), regeneration of the endometrium, and activation of innate immune defences leading to phagocytosis of bacteria by neutrophils. However, about 15% of dairy cows have clinical signs of uterine disease that persist beyond three weeks post partum. This is termed clinical endometritis and is characterised by purulent material in the uterus, which is usually detectable in the vagina (Fig. 1). These infections often involve a mixture of pathogenic bacteria such as *Escherichia coli*, *Arcanobacterium pyogenes*, and anaerobic bacteria such as *Fusobacterium necrophorum* and *Prevotella* species. There is massive infiltration of the endometrium and the uterine lumen with neutrophils, which can be detected histologically in biopsies or in fluid collected from the uterine lumen. In addition, there is often evidence of a wider immune response, with increased concentrations of pro-inflammatory cytokines and acute phase proteins in the peripheral circulation, but these animals rarely show signs of systemic disease.

There are several risk factors that have been associated with uterine infection with pathogenic bacteria and clinical endometritis. These factors can be categorised into those affecting the balance between the bacteria and immunity, uterine damage, and metabolic conditions, and examples are given in Table 1. The presence of pathogenic bac-

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teria in the uterine lumen and the associated inflammation of the endometrium preclude successful development and implantation of a viable embryo, so these animals can not conceive while they are affected. Furthermore, even after successful resolution of the clinical signs of uterine disease, these animals have lower conception rates. One possible explanation for this observation is that the uterine inflammation may persist after elimination of the bacteria from the uterine lumen. There may also be chronic scarring of the endometrium or adhesions of the oviduct that disrupt conception.

The uterine infection also appears to disrupt the endocrine function of the endometrium and luteolysis of the ovarian corpus luteum is often delayed. Luteolysis is induced by the release of prostaglandin F_{2α} from the uterine endometrium, which passes to the ovary from the uterus via localised vascular pathways, to initiate the destruction of the corpus luteum. However, during infection bacterial toxins bind directly to uterine epithelial and stromal cells to stimulate the release of prostaglandin E₂, which is luteotrophic and may prevent luteolysis. This may lead to a vicious circle because uterine infection tends to persist when concentrations of progesterone are high, whereas the follicular phase of the oestrous cycle is associated with enhanced uterine immunity.

Bacterial toxins and products of the inflammatory process in the uterus also pass into the peripheral circulation and have wider effects. Bacterial endotoxin and cytokines suppress the release of gonadotrophin releasing hormone (GnRH) from the hypothalamus, and disrupt the secretion of luteinising hormone (LH) from the pituitary. The net effect of this disruption of the overarching control centres for reproduction in the hypothalamus and pituitary is that there is failure of ovulation, increase cystic ovarian disease and anovulatory

anoestrus. Indeed, epidemiological studies of dairy herds support these associations between uterine disease and ovarian dysfunction. As well as effects of the inflammatory products on the control centres in the brain, there may also be direct effects on the ovary. Uterine disease is associated with slower growth of ovarian follicles and their function is compromised, as judged by reduced oestradiol secretion. This disruption of ovarian function is likely to further compromise fertility and reduce conception rates.



Figure 1

Clinical endometritis is characterised by purulent material from the uterus detectable in the vagina or discharging from the vulva of cattle that are at least 3 weeks post partum.

Consequences of endometritis

As uterine infection exerts detrimental effects at all levels of the reproductive system, it is not surprising that it causes considerable disruption of fertility in cattle. Even when animals are treated, the conception rate is about 20% lower for cows with endometritis, the calving to conception interval 30 days longer and there are 3% more animals culled

for failure to conceive. As well as the effects on fertility, uterine infection is associated with lower milk yields particularly if it is associated with retained placenta. The financial losses associated with uterine infection are dependent on the cost of treatment, reduced milk yield, and subfertility. In the UK, the direct costs of treatment and reduced milk yield are about £60, and the indirect costs of extra inseminations, a longer calving interval and increased culling rate are about £70.

Approach to endometritis diagnosis and treatment

The first question to address is whether it is necessary to treat endometritis. Most cows that acquire bacterial contamination of the uterine lumen after parturition eliminate those bacteria within 3 weeks of calving. Even after that, a range of immune mechanisms continue to operate against bacteria contaminating the uterus. Thus, it has been argued that endometritis should be allowed to resolve spontaneously. Treatment of bacterial contamination of the uterus during the first 3 weeks post partum seems superfluous in the face of the substantial changes associated with uterine involution and regeneration of the endometrium. Although, it is essential to remember that animals with puerperal metritis need veterinary intervention. After 3 weeks post partum, the localised infection of the uterus is usually associated with the persistence of pathogenic bacteria rather than opportunistic contaminants. In addition, if the animal is diseased at this point the spontaneous recover rates over a two week period are only about 33%, which is about half that expected with veterinary treatment. If animals with clinical endometritis are not treated the implication would be that half the animals with endometritis at three weeks post partum would still have clinical signs by 7 weeks, when farmers usually start inseminating cattle. Thus, treatment from three weeks has been shown to be beneficial for subsequent herd fertil-

ity. Finally, there is a welfare concern if treatment is not instituted, because two of the five “Freedoms” are compromised: freedom from disease and freedom from pain or suffering. Although the pain associated with uterine disease has not been well characterised, our clinical experience is that affected animals often have a reduced appetite and milk production. On balance, it would seem prudent to identify and treat animals with clinical endometritis from about three weeks post partum.

Diagnosis of endometritis

To diagnose clinical endometritis the contents of the vagina should be inspected for the presence of pus. Vaginoscopy can be performed using autoclavable plastic or disposable foil-lined cardboard vaginoscopes, which allow inspection of the mucus flowing out of the cervix, but they tend to be inconvenient. A new device for examination of vaginal mucus (Metricheck®, Simcro, New Zealand) consists of a stainless steel rod with a rubber hemisphere that is used to rake out the vaginal contents. However, our routine method for examination of the contents of the vagina, is to perform a manual examination and withdraw the mucus for inspection. The vulva is cleaned using a dry paper towel and a clean, lubricated gloved hand inserted through the vulva into the vagina. The walls of the vagina and the external cervical os are palpated and the mucus contents of the vagina withdrawn for examination. The advantage of this technique is that it is cheap, quick, provides additional sensory information such as detection of vaginal lacerations, and allows quantification of the volume and detection of the odour of the mucus in the vagina.

The character and odour of the vaginal mucus can be scored to produce a clinical endometritis score. The vaginal mucus character is assessed for colour and proportion of pus. A mucus character score is assigned between 0, clear translucent mucus; 1, clear mucus con-

Balance between bacteria and immunity	Disruption of neutrophil function Bacteria in the uterine lumen such as <i>E. coli</i> and <i>A. pyogenes</i> Progesterone or glucocorticoid administration Early formation of a corpus luteum Hygiene of the cows, calving boxes and environment
Uterine damage	Stillbirth, twins, dystocia. Retained fetal membranes Delayed uterine involution
Metabolic conditions	Milk fever Ketosis and negative energy balance Micronutrient deficiencies

Table 1

Risk factors for the establishment of clinical endometritis

taining flecks of white pus; 2, discharge containing $\leq 50\%$ white or yellow-white pus; 3, discharge containing $\geq 50\%$ white, yellow-white or bloody pus (Fig. 2). The vaginal mucus odour is scored 0 for no odour and 3 if a foetid odour is present. The character and odour scores are summed to give a clinical endometritis score ranging from 0 to 6. Although few animals with a mucus character score of < 3 also have a foetid odour, weighting the foetid odour score as 3 avoids the potential confusion that might occur if the score was 1.

The character score also reflects the presence and number of recognised uterine pathogens such as *E. coli* and *A. pyogenes*, but not potential pathogens or opportunist contaminants. A foetid odour of the vaginal mucus is similarly associated with infection with uterine pathogens, but not other bacteria. More importantly for the veterinarian, the clinical endometritis score is prognostic for the likely success of treatment. The success rate for cure of endometritis over a two-week period was 44% if the vaginal mucus was purulent with a foetid odour, but 78% for a clinical endometritis score of 1.

The selection of animals for veterinary examination can be based on a strategic

or a blanket policy. A strategic approach would be to inspect animals where the farmer has observed a purulent vulval discharge and/or the presence of a risk factor event in an animal's clinical history (Table 1). The alternative blanket approach is to examine each animal once they have been calved at least three weeks. This system is most easily adopted where veterinarians perform routine herd fertility visits on a regular basis, so that several animals can be inspected at the same time. Thus, if routine visits are performed every two weeks, all animals calved between three and five weeks are selected for examination and this is our preferred approach for well organised farms.

Treatment of endometritis

The development of treatments for endometritis has relied on taking advantage of the cows innate immunity and the use of antimicrobial products. Oestrus is associated with spontaneous resolution of disease, whilst uterine immunity is suppressed during the luteal phase. Thus, if a corpus luteum is present in an ovary of affected animals, the injection of prostaglandin F₂ α or analogues, is a highly effective treatment. Administration of oestrogenic compounds to food producing animals is prohibited in the EU, and although in

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the past oestradiol often improved the clinical disease, the interval to conception was longer than for animals where oestrus was induced. It is likely that the reduction in progesterone concentration and the events associated with oestrus are as important as the increased oestradiol concentrations after luteolysis. Prostaglandin F_{2α} analogues have the benefit of infinitesimal residues, so are extremely unlikely to compromise food quality.

Intrauterine administration of an antimicrobial compound is the alternative to prostaglandin F_{2α} and is particularly valuable when a corpus luteum is not present in the affected animal. Many antimicrobial compounds and antiseptics have been infused into the bovine uterus. The compound chosen should be effective against the pathogenic bacteria in the uterine lumen environment and not compromise uterine immunity or require withdrawal of milk for human consumption. Currently cephalosporins meet these criteria and have replaced oxytetracycline. Bacterial resistance to oxytetracycline is common and the doses required to achieve a minimum inhibitory concentration are far greater than those for the cephalosporins.

An unanswered question about the treatment of endometritis is whether multiple treatments are beneficial, although many veterinarians use this approach. A combination of intrauterine cephalosporin at the same time or after prostaglandin F_{2α} may be more effective than the single components, and at least is unlikely to cause harm, although a common protocol is yet to be agreed. However, veterinarians should be extremely cautious if they administer two doses of intrauterine antibiotic concurrently, as there is a risk of exceeding the minimum residue limit.

Subclinical endometritis

Subclinical endometritis is an emerging area of investigation and can be defined as inflammation of the uterus

that results in significant reduction in reproductive performance in the absence of overt clinical signs. Subclinical endometritis is diagnosed by measurement of uterine inflammation using the proportion of neutrophils present in a uterine cytology sample collected by flushing the uterine lumen or using a cytobrush, in animals without clinical endometritis. Some of these animals may have pathogenic bacteria in the uterus, although there is insufficient pus in the vagina to diagnose clinical endometritis. Alternatively, the bacteria may have been eliminated from the uterus, but endometrial inflammation persists. In the USA, Gilbert and others (2006) reported a prevalence of clinical and subclinical endometritis of 53% at 40 to 60 days postpartum, which was associated with delayed conception and increased culling. The mildest category of subclinical endometritis was 5 to 10% neutrophils and even this group had longer calving to conception intervals compared with unaffected animals. Although it is early days in the evaluation and validation of subclinical endometritis, a working definition is the presence of > 18%, > 10%, or > 5% neutrophils in uterine cytology samples collected 20 to 33, 34 to 47 days, or after 50 days post partum, in the absence of signs of clinical endometritis. The next issue is whether these animals should be treated, and on the basis of the compromised fertility the implication is that they should be.

Control of endometritis

Little progress has been made in terms of a structured approach to the control or prevention of bovine endometritis. The risk factors that have been associated with uterine infection include abortion, dystocia, twins, retained fetal membranes and metabolic disease. On the other hand factors that intuitively might have been thought to influence the severity or incidence of disease such as the hygiene of the farm environment have proved difficult to confirm. As a consequence, there are few control

programmes for preventing uterine disease and the approach to investigation of a high incidence of uterine disease is often to empirically evaluate each of the known risk factors in turn. However, often there is little that can be done to intervene during problems caused by factors such as dystocia.

Common thoughts on the control of endometritis focus on attention to detail and optimising animal husbandry. Thus, paying attention to the hygiene of cattle accommodation and calving facilities will pay dividends in terms of cleaner surfaces for animals to lie on, and less contamination of the skin and hair of the animal with bacteria. Formulation of the diet is important for several reasons. There is some evidence that negative energy balance or deficiencies of micronutrients such as selenium and Vitamin E can suppress immunity. Perhaps of greater importance is that the liquid faeces common in many dairy herds likely contributes to bacterial infection of the genital tract as the vulva is often plastered with dung. Indeed, it is intriguing to note that beef cattle usually have more formed faeces with less contamination of the vulva, and less endometritis.

Conclusions

Uterine infection is common in cattle after parturition and causes considerable infertility. Veterinary diagnosis is straightforward, as long as the contents of the vagina are inspected, but a herd health strategy for selection and examination of cows is required. Evaluation of the severity of endometritis adds value to the veterinary examination, and reflects the presence of pathogenic bacteria and the likelihood of the success of treatment. The most common treatments are the induction of oestrus using prostaglandin F_{2α} if a corpus luteum is present in an ovary, and/or the administration of antimicrobials into the uterine lumen. Both treatments are reasonably effective for resolving the clinical signs of disease, but



Figure 2

Typical samples of vaginal mucus with a character score of 1, mucus containing flecks of white or off-white pus; 2, mucus containing $\leq 50\%$ white or off-white purulent material; and 3, discharge containing $\geq 50\%$ purulent material, usually white or yellow, but occasionally sanguineous.

the effects of sub-clinical endometritis are yet to be fully characterised. The outstanding challenge is to develop strategies to control and prevent clinical endometritis.

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Further information

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Uterine disease website at www.rvc.ac.uk/AboutUs/Staff/Sheldon/index.cfm

In the next issue:

Next issue of the Intervet Reproduction Newsletter will be devoted to the management of oestrus in beef cattle. Dr. Rene Fourier will give us the highlights of the physiological determinants for our possibilities in the manipulation of oestrus cycle in beef cows. The article will contain also an overview of the methods currently used for oestrus induction and synchronization in beef cows and heifers of European breeds with practical recommendations and indication of the success rates observed in the field.