Bovine neonatal pancytopaenia in New Zealand

Mark Bryan
VetSouth, Winton, Southland

Introduction

Bovine Neonatal Pancytopaenia (BNP) is a new, rare syndrome which emerged in young calves in Europe in 2007, and was diagnosed for the first time in New Zealand in 2011. Commonly called ‘bleeding calf disease’, the syndrome was first formally reported in 2009 in the UK (Penny et al. 2009), although it is believed to have first occurred as early as 2007 (Bell 2011), and possibly 2006 in mainland Europe (Baker 2012).

The disease is characterised by signs of obvious external, or less commonly, internal, haemorrhage in calves less than four weeks of age. The disease affects both beef and dairy calves, and the outcome is invariably fatal.

The aetiology of the disease is not fully understood, although European studies have led to the proposal of an alloantibody response to MHC 1 in calves, associated with the use of a specific BVD vaccination in dams (Deutskens et al. 2011).

BNP overseas

History

Unconfirmed reports have suggested that BNP was first diagnosed in Germany in 2007 and in Belgium in 2006 (Baker 2011). In 2007-8, the Scottish Agricultural College reported unexplained deaths in newborn calves. In 2009, 41 cases on 32 farms were reported in Scotland; and 57 cases on 42 farms in England and Wales. In 2010, there were 91 confirmed cases in Scotland alone. Of these, 77 were in beef calves; and the remainder dairy.

By early 2011 200 farms across the UK had been reported as being affected, and by late 2011 around 4000 calves had been reported as being affected across Europe (Bastian et al. 2011). Most recent data has reported around 5600 suspect cases in Europe (PAH pharmacovigilance 2012). Only Switzerland and Scandinavia remain unaffected in Europe, whilst other continents with the sole exception of NZ, have not reported the disease as yet (Friedrich et al. 2011).

Clinical signs

The disease is typically sporadic, and rare, although cases where up to 5% of calves have been affected on a single farm have been reported (Bell et al. 2011). Affected calves are typically 2-3 weeks of age, and virtually always less than four weeks of age.

Typically, affected calves are otherwise normal with no history of previous disease. Affected calves show evidence of widespread haemorrhage, which may manifest externally as bleeding from ear tag and injection sites, from gums and from the nose, sometimes from the mouth and tongue; with or without melaena. Obviously, calves are at risk of bleeding from any trauma, particularly intra-oral lesions. Haematomas are not uncommon. In Germany, calves have been reported to spontaneously bleed from the skin (Friedrich et al. 2009a), although this is less commonly reported elsewhere, and may be related to fly bites.
Internal bleeding may occur in tandem with external haemorrhage, or it may be the sole symptom. Thus, calves may present with signs of acute circulatory collapse, such as dyspnoea, pale mucous membranes and petechiation.

Affected calves are normally markedly pyrexic (>40°C), and the pyrexia is normally non-responsive to therapy. Death normally occurs within seven days, although a small proportion (<10%) of calves may survive and fully recover.

The haematological picture is typical, and illustrates the marked anaemia seen in calves (Table 1). There is a profound thrombocytopenia and leucopaenia, due to both a neutropaenia and lymphopaenia. Many cases also have a normocytic, normochromic, non-regenerative anaemia. Calves that recover may experience lesser levels of anaemia.

Calves may be born to heifers or cows. However, dams are clinically normal. It has been suggested that dams of BNP calves may have further BNP calves in the subsequent lactation (Pardon et al. 2010).

Post mortem is typically dramatic and reveals widespread haemorrhage throughout the body, often including severe bruising and petechiation, particularly around areas of contact. Haematology is highly suggestive of the diagnosis, but a definitive diagnosis requires bone marrow histopathology.

**Treatment**

Treatment is largely supportive, and ineffectual. However, a small proportion of calves have been reported to survive. Whole blood transfusion may be attempted, as long as this is not from the dam; and corticosteroids, NSAIDs and antibiotics have all been used. The critical risk is with haemorrhage from handling and in particular from needle punctures, which limits the efficacy of aggressive supportive treatment.

**Incidence**

The reported overall incidence is low, at 16 cases in every 10,000 calves (Defra 2011). The latest pharmacovigilance data from doses sold and the number of animals treated suggests 14.9m doses were used in approximately 5m animals, with 5600 suspected calves reported but not confirmed (PAH, pers comms). This makes an incidence rate of 1.1 calves per 1000. There is a marked geographic difference: in Germany it was 1 in 800 calves; Republic of Ireland it was 1 in 28000 doses; in the UK it was 1 in 7000.

**BNP in New Zealand in 2011**

**History**

In August of 2011, a veterinarian in Rotorua was called to post mortem a calf which had been listless for a couple of days and, according to the owner, had presented some epistaxis. The veterinarian performed a post mortem and strongly suspected BNP, due to the unusual amount of internal haemorrhage and the history of BVD (PregSure) vaccination. Pfizer Animal Health were contacted and NCDI were also involved. This calf was subsequently confirmed as BNP and became the index case in New Zealand.

**Incidence**

Over the following weeks, a total of 77 suspect cases of BNP were reported across New Zealand. Of these, 27 cases were confirmed (35% of suspected cases); 15 were confirmed as not being BNP (20%); and in 35 cases (45%) a diagnosis was not reached. There is no denominator data for these cases, so a true incidence is hard to establish. Most were simply sick calves reported as a consequence of the increased awareness of the disease and heightened vigilance.

Subsequently, cases of BNP were confirmed on 17 farms across New Zealand. Sixteen of these farms had a history of BVD vaccination with PregSure™. The sole farm that had no definitive PregSure™ history, nevertheless had a complex recent history, being put together from four different herds with incomplete records. The mean case incidence was 1.7 on affected farms (range 1-5).

All calves were less than 3 weeks of age at diagnosis. The age range was 8-21 days, with a mean of 15 days. The mortality rate was 26/27 (95%). Age was reported in only 13 of the 27 dams involved, and ranged from 2-10 years, with a mean of 4.7 years. Death usually occurred within 24 hours of clinical examination, in contrast to
the more delayed progression seen in Europe. This may be a function of poorer observation over larger numbers of calves in New Zealand; or it may be a consequence of more recent dam vaccination.

Twenty-six of the 27 dams had been vaccinated with PregSure™, one had not. The most recent vaccination for most (15/27) dams was pre-mating 2010 (i.e. approximately 10 months prior to the development of BNP in the calf). However, nine dams had been vaccinated as recently as pre-calving in 2011; and two had been last vaccinated in the pre-mating period of 2009. Thus, 92% (24/27) of cases occurred within 12 months of being vaccinated (in Europe approximately 80% of dams have been vaccinated within 12 months).

It is worth noting that a third of the cases (9/27) were from dams vaccinated pre-calving. Product sales data is such that this proportion is far higher than the proportion of product sold at this time of year compared to total, indicating that dams vaccinated pre-calving are over-represented in the disease.

The incidence data in New Zealand from a pharmacovigilance perspective would suggest that approximately 300,000 cows were vaccinated and calves last spring, and with 27 confirmed cases the incidence rate is around 1 in 10,000; and of reported cases around 2.5/10,000 calves. The clinical picture is similar to that described in Europe. The key differences are the not unexpected temporal clustering of cases, given the seasonality of dairy farming in New Zealand; and the apparently more rapid progression of the disease from initial clinical signs.

In both Europe and in New Zealand, spatial clustering was observed. In Europe it was more at a country level- ie, Germany and Scotland had higher incidences of cases. In New Zealand it was more localised, with clustering in areas such as Rotorua and Waimate. This may be the effect of increased awareness, or of vaccination patterns. However, given the theoretical model below, the potential genetic effect of specific bulls is also possible.

**Proposed aetiology and pathogenesis**

A model for the pathogenesis of the syndrome has been proposed. The disease has been found to be strongly associated with the use of PregSure™ vaccine in the dam. The risk to a calf of developing BNP when born to a dam vaccinated with PregSure™ is reported as being 10 times that of a calf where the dam is not vaccinated (Defra 2011).

Recent work has led to the development of a model suggesting a vaccinated dam develops alloantibodies to MHC 1 (Deutskens et al. 2011). It is believed that affected calves carry a paternally derived MHC 1 variant allotype, which is similar to that found within PregSure™, and which in turn is targeted by maternal alloantibodies. The antigen is found normally on bovine kidney cells, and is present on all mammalian blood cells except red blood cells. The process of vaccine development appears to lead to the inclusion of this protein in the vaccine, which in turn triggers an alloantibody response.

A critical 44kDa protein present as a constituent of the vaccine was found to be MHC 1. Colostrum produced from dams vaccinated with PregSure™ is thus at risk of containing alloantibodies to MHC 1, which binding of the alloantibodies will lead to complement dependent lysis and/or preferential cytophagocytosis (Bastian et al. 2011) of cells expressing high levels of antigen.

Recently, a subclinical version of the syndrome was discovered (Witt et al. 2011), leading to the suggestion that the effect BNP is moderated by the strength of exposure to colostrum containing alloantibodies. Thus, disease appears to depend on the time from vaccination with PregSure™; the quantity of affected colostrum ingested; and the inheritance of a paternally derived MHC 1 variant.

The model proposed allows for a dose-dependent response, which can occur where colostrum intake is high or low; or where vaccine is administered at various times relative to calving.

As a precautionary measure, the vaccine was withdrawn by Pfizer from wholesale sales in the UK market in June 2010; and a full product recall was instigated in New Zealand in September 2011 (PAH, pers comm.).

It is worth noting that the incidence in Europe hasn’t been decreasing as fast as expected- this is thought to be because of the volume of stock remaining in clinics and on farm, compared to the New Zealand situation where the product was physically recalled from circulation.

**Conclusion**

The discovery of BNP in New Zealand was the first discovery of BNP outside of Europe, and remains the only
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Identification outside of Europe. It is likely that the reported incidence was lower than the true incidence by virtue of the fact that the syndrome was new to New Zealand and therefore liable to be underdiagnosed. Furthermore, many calves in New Zealand who could potentially have been affected may have been removed from the farm as ‘bobbies’, within seven days of birth; or may have been born dead to induced calves. Subclinical disease was not reported in New Zealand, but again, may well not be recognised.

It remains to be seen whether further cases will be experienced this spring. Data from overseas would suggest the incidence would likely be much lower as the time from vaccination increases. Veterinarians are asked to be aware of the possibility of further clinical cases; and also of the possibility of subclinical cases, and to report any suspect cases of either wherever possible. The most likely herds to be at risk are those where the vaccine was given pre-calving in 2011.

Acknowledgements

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References


Bell C. Bovine neonatal pancytopenia or bleeding calf syndrome. UK Vet 16 (1), 24-28, 2011


Pfizer Animal Health. Personal communication, 2012

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*Table 1. Typical Haematological values of calf with BNP*