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Calf Pneumonia

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This article describes infectious calf pneumonia, which is a high-morbidity pneumonia seen most frequently in housed dairy animals. Many outbreaks occur in the initial housing period when the calves are only a few weeks or months of age. However, calves born in the spring and pastured during the summer may also develop pneumonia when housed the following autumn.

The term infectious calf pneumonia is a very general one and embraces a range of pulmonary lesions caused by various microorganisms. Although infectious agents are responsible for the lung damage, environmental factors often markedly predispose to and increase the severity of outbreaks.

ETIOLOGIC AGENTS

Viruses, myoplasmas, and bacteria are involved in the production of lung damage and in outbreaks investigated at an early stage, all three agents may be demonstrable in the upper and lower respiratory tract of affected animals.

Viruses

Many viruses have been recovered from or associated with calf pneumonia outbreaks, and the list is likely to lengthen in the future. Concurrent infection with two or more viruses is frequently demonstrable in the same outbreak. Viral activity has been reported most frequently in the early stages of outbreaks of acute pneumonia, and it would appear in many cases that primary virus infection initiates the outbreak, producing respiratory tract damage that is subsequently extended by mycoplasmas and secondary bacterial infection. Whether viral activity occurs in every outbreak of calf pneumonia is unknown, but undoubtedly in the past many infections have not been detected because of improper timing of sampling and submission of unsuitable or inadequate specimens to the diagnostic laboratory. In one

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237
survey of 38 outbreaks of calf pneumonia investigated at an early stage, viral activity was demonstrable in 27 (70 per cent). 64-68

The viruses that have been most frequently recovered from outbreaks of calf pneumonia are parainfluenza-3 virus (PI-3 virus), respiratory syncytial virus (RSV), and bovine virus diarrhea/mucosal disease virus (BVD/MD virus). These agents are widely distributed in the cattle population of most countries, and serologic surveys in various American states have revealed a high prevalence of antibody to them. 40,65 In a 3-year longitudinal study of respiratory viral infection on a large calf-rearing unit, although a number of different viral infections, including reovirus, rhinovirus, enterovirus, and adenovirus, were identified, only PI-3 virus and RSV infections were shown by statistical analysis to be significantly associated with outbreaks of respiratory disease. 49 Calf challenge experiments have shown that strains of both PI-3 virus and RSV can produce extensive pulmonary consolidation when inoculated into calves, with the most severe lesions being produced in seronegative calves less than 6 months old (Fig. 1). 9,11,37

Following experimental infection, PI-3 and RSV replicate in epithelial cells of both the upper and lower respiratory tract, and virus may be present in nasal secretions for up to 20 days following infection. Replication of virus in epithelial cells of the lower respiratory tract causes bronchitis, bronchiolitis, and alveolitis of varying severity. In the acute stage of virus infection, there is proliferation and necrosis of bronchiolar epithelial cells with widespread destruction of cilia and of ciliated cells in small bronchi and bronchioi. 10 Hyperplasia of alveolar epithelial cells may be extensive, and epithelial syncytia are often formed on bronchiolar and alveolar walls. Both viruses infect alveolar macrophages, and viral interference with alveolar macrophage function may be a major predisposing factor to secondary bacterial pneumonia. 57,58 In the repair stages of severe PI-3 virus or RSV pneu-
monia, there is widespread organization of bronchiolar exudate, leading to the formation of residual fibrous masses within bronchiolar lumina.9-11

The clinical picture seen in many experimental and naturally occurring PI-3 or RSV infections is of only mild or moderate severity. However, severe outbreaks of pneumonia associated with RSV or a combination of RSV and PI-3 virus infection also occur. These are seen most commonly in the fall, and calves from 1 month old to yearlings may be affected; in an affected group, up to 20 per cent of calves may rapidly develop severe respiratory distress. The pathologic and microbiologic findings in the lower respiratory tract of these severely affected animals are indicative of an extensive virus pneumonia.8,39

BVD/MD virus is not uncommonly detected in the nasal secretions and lungs of calves with pneumonia, and development of antibodies to this virus may occur in association with outbreaks of calf pneumonia. Mild clinical signs of respiratory disease and small scattered areas of interstitial pneumonia have been observed following endobronchial inoculation of calves with BVD/MD virus.41 Numerous bacteria were present in the lower respiratory tract of some of these experimental animals, indicating that BVD virus infection impaired bacterial clearance. A severe respiratory illness with extensive fibrinopurulent pneumonia developed in calves sequentially inoculated with BVD/MD virus and, 5 days later, with Pasteurella haemolytica.41 Such studies on the pathogenesis of BVD/MD virus infection of the bovine respiratory tract have been all too rare, and further experimental work is necessary to clarify the role of this virus in outbreaks of calf pneumonia.

On occasion, adenoviruses, rhinoviruses, reoviruses, enteroviruses, and herpesviruses have also been recovered from outbreaks. Recently, corona-viruses have been isolated from the trachea and lungs of young calves with pneumonia.31 To date, however, with the exception of bovine adenovirus type 3,14 the clinical disease and lower respiratory tract damage produced by these viruses experimentally has been less severe than that associated with RSV or PI-3 virus. Bovine herpes-virus type 1 (infectious bovine rhinotracheitis virus) is recovered only rarely from the pneumonic lungs of young calves. The major effect of this virus is exerted in the upper respiratory tract, and bovine herpesvirus 1 does not play a major role in outbreaks of calf pneumonia.

Mycoplasmas

Mycoplasmas are frequently recovered from the upper and lower respiratory tract of calves in both early and later stages of pneumonia outbreaks. The Mycoplasma sp. most commonly isolated from pneumonic lungs are M. dispar, M. bovis, ureaplasmas, and M. bovirhinis. M. bovigenitalium has also been isolated on occasion. Mixed infections with two or more Mycoplasma sp. are common. Although mycoplasmas may also be recovered from the upper and sometimes the lower respiratory tract of nonpneumonic calves, the frequency of isolation is much greater from the pneumonic respiratory tract.

Mycoplasma infections have often been associated with peribronchial and peribronchiolar lymphoid hyperplasia in animal species, and in calves a significant association has been noted between M. dispar and “cuffing
pneumonia," which is a pneumonia characterized by an expanding peribronchial sheath of lymphoid cells.\textsuperscript{1} However, mycoplasmas, including \textit{M. dispar}, are also frequently recovered from lesions of acute and chronic bronchopneumonia in calves in which peribronchial and peribronchiolar lymphoid hyperplasia has not been pronounced.\textsuperscript{7}

Experimentally, strains of \textit{M. dispar}, ureaplasmas, \textit{M. bovis}, and \textit{M. bovigenitalium} singly and in combination have produced pneumonia when inoculated into the lower respiratory tract of experimental calves.\textsuperscript{16,18,19,22,42} Histologic examination of the experimental pneumonia has revealed purulent bronchiolitis, variable degrees of peribronchial and peribronchiolar lymphoid hyperplasia, thickening of alveolar septa due to cellular infiltration, and alveolar collapse. In most experimental infections, lung lesions produced by mycoplasmas have been very limited in extent, and clinical signs have been mild and frequently absent. Therefore, doubt has been expressed as to whether mycoplasmas alone, in the absence of viral and secondary bacterial infections, can produce lung lesions of comparable severity to those seen in naturally occurring outbreaks. Synergism has been demonstrated between \textit{M. bovis} and \textit{P. haemolytica} in calf pneumonia, but the mechanism of the synergistic effect is not understood.\textsuperscript{21} Future studies must consider virus/mycoplasma and mycoplasma/bacteria interaction in the bovine lung if the pathogenesis of calf pneumonia is to be fully understood.

\textbf{Bacteria}

Pathogenic bacteria play an important role in many outbreaks of calf pneumonia. Significant isolates have been \textit{Pasteurella} sp., \textit{Haemophilus somnus}, \textit{Corynebacterium pyogenes}, and \textit{Streptobacillus actinoides}. Mixed infections are not uncommon. \textit{Pasteurella multocida} and \textit{Haemophilus somnus} organisms are often recovered in large numbers from the lungs of calves dying with severe exudative bronchopneumonia. \textit{C. pyogenes} is frequently associated with chronic suppurative pulmonary disease including lung abscesses and bronchiectasis.

\textit{Pasteurellae}, particularly \textit{P. multocida} and less commonly \textit{P. haemolytica}, are the bacteria most consistently recovered from the pneumatic lungs of young calves. These organisms are rarely recovered from lungs of nonpneumonic calves but may be present as part of the bacterial flora of the nasal passages and nasopharynx of healthy calves. Their role in calf pneumonia is mainly a secondary one, extending and increasing the severity of primary lung damage caused by viruses and/or mycoplasmas and frequently causing acute exacerbation of clinical signs that may terminate fatally.

Pneumonia is not an uncommon clinical finding in outbreaks of salmonellosis in cattle, and extensive exudative and necrotizing lung lesions have been noted in outbreaks of \textit{S. dublin} and \textit{S. enteriditis} disease in calves.\textsuperscript{7,38} Whether \textit{Salmonella} sp. are on occasion capable of producing primary pneumonia in calves is not clear. However, salmonellosis superimposed on calves with pre-existing pneumonia will certainly cause exacerbation of clinical signs and pulmonary damage.
Calf Pneumonia

EPIDEMIOLOGY

Outbreaks of pneumonia are common in groups of calves reared indoors; problems occur in dairy units, intensive beef-calf rearing units, and cow-calf operations in which the cows and calves are housed indoors in winter. Outbreaks may occur at any time of the year but are particularly common in the fall and early winter periods. This seasonal incidence is particularly noticeable with PI-3 virus and RSV infections.

Calves with pneumonia excrete viruses and mycoplasmas in nasal secretions and in aerosols produced by coughing. When susceptible young calves are introduced into a house in which there are already older animals with pneumonia, the recently introduced stock will be infected by a combination of short-range airborne spread and nose-to-nose contact. Such a situation occurs on several dairy farms where calving is spread over a period, accommodation for young calves is limited, and where, consequently, calves of different ages are likely to be mixed together in the same airspace.

Outbreaks of pneumonia also occur in batches of calves of uniform age that are introduced into houses that may have been previously disinfected and left empty for a period or that may never have held calves. In these circumstances, the source of infection is harder to comprehend, and several factors appear to be important:

1. A proportion of calves may be infected with respiratory pathogens at a very early stage in life. PI-3 virus and RSV excretion has been detected in colostrum-fed calves only a few days of age and in a small proportion of colostrum-deprived calves removed from farms at birth and raised under isolation conditions. Such excretion is usually associated with mild signs of respiratory disease that may well be missed under field conditions. PI-3 virus has on occasion been isolated from aborted bovine fetuses, and antibody to PI-3 virus and to RSV has been detected in bovine fetal fluids. Naturally occurring pneumonia has been observed in bovine fetal lungs and in the lungs of unsuckled calves only a few hours old, and histologic lesions suggestive of paramyxovirus disease have been described. Udder infection, with excretion of virus in milk, has been described in naturally occurring PI-3 virus infections of cows, and the strains involved produced respiratory disease when inoculated into calves. These observations indicate that congenital or very early neonatal infection with respiratory viruses can occur. Genital and udder infection of the dam may also occasionally be a source of early M. bovis, ureaplasma, or M. bovigenitalium infection for the young calf. A proportion of calves, therefore, may already be infected with respiratory pathogens before being incorporated into a self-contained group and can subsequently disseminate infection to their comrades.

2. Outbreaks of pneumonia may occur when the same group of animals has been together for weeks or months with no history of previous illness, with no changes in management or introduction of new stock, and sometimes under experimental isolation conditions. Such incidents may be triggered by activation of persistent or latent virus infection within the respiratory tract. The factors influencing activation in the natural situation are not fully understood, but factors such as waning of maternal antibodies, the stress of sudden temperature swings, changes in weather conditions, or decreased dietary protein intake after weaning leading to reduced pro-
duction of interferon within the respiratory tract have all been suggested.\textsuperscript{35,36}

3. The possibility of cross-infections between species must also be considered. Experimentally, calves have been successfully infected with ovine\textsuperscript{48} and human\textsuperscript{48} strains of PI-3 virus and with human strains of RSV.\textsuperscript{48} In lambs, bovine strains of PI-3 virus\textsuperscript{48} and RSV\textsuperscript{58} have produced clinical respiratory disease and pneumonia. Therefore, the possibility exists that cross-infections with respiratory viruses, particularly between cattle, sheep, and humans, occur naturally and are important.

Although infectious agents are the major factors in the infliction of respiratory tract damage, there is no doubt that environmental conditions can have an important influence on the severity of pneumonia outbreaks. Although good housing is no guarantee of freedom from pneumonia, respiratory problems are likely to be of maximum severity under conditions of bad housing. Environmental factors facilitating the incidence and spread of infectious respiratory disease include overcrowding of calves in the same airspace, inadequate ventilation leading to a build-up of microorganisms and irritant waste gases, large temperature fluctuations within the house, drafts at stock level, and houses that are never empty and within which, therefore, there is persistent infection.\textsuperscript{6,43} A high incidence of respiratory disease in young calves has been associated with a cubic airspace of less than 5.66 m\textsuperscript{3} per calf.\textsuperscript{57}

**CLINICAL, PATHOLOGIC, AND MICROBIOLOGIC FINDINGS IN CALF PNEUMONIA**

In units in which calves are being reared there will usually be a background of sporadic coughing that will be particularly evident in large groups of animals. Such coughing may not be associated with any apparent ill effect on the calves, and clinical examination may reveal little evidence of lower respiratory tract damage. In some instances, this may be the total extent of the respiratory problem, and veterinary attention may never be sought. Frequently, however, outbreaks of pneumonia occur. These may be of sudden or insidious onset, and the veterinary clinician, pathologist, and microbiologist may be consulted at an early or late stage.

**Sudden-Onset Acute Pneumonia Outbreaks**

These are seen in groups of calves from 2 weeks old to yearlings, but most primary outbreaks occur in groups of calves aged 2 to 6 months. Over a period of 1 or 2 days, there is an increased frequency of coughing, with several calves developing noticeable tachypnea and hyperpnea. Auscultation reveals increased harshness of lung sounds cranioventrally. A serous or sero-purulent nasal discharge is common, and the most severely affected animals may be pyrexic.\textsuperscript{6,65} Virus is frequently demonstrable in the upper respiratory tract of calves at this stage.

In the majority of outbreaks, deaths are uncommon at this time unless severe bacterial exudative pneumonia develops in individual animals. In the fall, however, severe outbreaks occur in which up to 20 per cent of calves
in a group may develop severe respiratory distress with dyspnea within the first week of the outbreak (Fig. 2). Examination of dyspneic animals reveals very harsh lung sounds craniocaudally with emphysematous crackles frequently detectable. Subcutaneous emphysema may be palpable. Response to antibiotic therapy is poor and fatalities occur. These outbreaks represent a particularly severe form of RSV or of a combined RSV and PI-3 virus infection. This syndrome was first described in Europe and termed “pinkengriep” or “yearling influenza.” Its incidence, however, is by no means restricted to yearlings; outbreaks occur commonly in groups of calves that are 2 to 6 months of age.

Pathologic and Microbiologic Findings in Early Stages of Acute Pneumonia Outbreaks

Sacrifice of coughing tachypneic calves in the early stage of pneumonia reveals red consolidated areas of varying extent in the cranial, middle, and accessory lung lobes. Virus(es), mycoplasmas, and small numbers of bacteria may be demonstrable in pneumonia lesions at this early stage. Histologic examination reveals bronchiolitis and alveolitis. Where PI-3, RSV, or adenovirus infection is present, hyperplasia and necrosis of bronchiolar epithelium may be prominent and inclusion bodies may be detectable in bronchiolar or alveolar epithelial cells. In some PI-3 and RSV infections, epithelial syncytia may be observed on bronchiolar and alveolar walls.

Necropsy of dyspneic calves from severe RSV or RSV and PI-3 virus pneumonia outbreaks reveals extensive dark red consolidation in the cranial, middle, accessory, and anterior parts of the caudal lung lobes with severe interstitial emphysema. Subpleural emphysema is usually visible in all affected lobes, and large dissecting emphysematous bullae are commonly present in the caudal lobes (Fig. 3). Hemorrhages are observed on the surface of the lungs and within bullae. Microscopic examination reveals severe bron-
chiolitis and alveolitis with an intense cellular infiltration into alveoli, alveolar edema, thickening of interalveolar septa, and alveolar epithelial hyperplasia. Epithelial syncytia containing eosinophilic intracytoplasmic inclusion bodies are usually observed on bronchiolar and alveolar walls, and detached syncytia may be seen in bronchiolar and alveolar exudate (Fig. 4). Many small airways are completely plugged with exudate. The histopathologic changes indicate a major viral contribution to the lower respiratory tract damage, and RSV or a combination of RSV and PI-3 virus antigen is usually demonstrable.

Figure 3. Fatal RSV pneumonia. Note consolidation in the anterior lobes, subpleural emphysema, and bulla formation in the caudal lobe (arrow).

Figure 4. Epithelial syncytia on alveolar walls. Some contain intracytoplasmic inclusion bodies (arrows) (H and E stain).
in the lungs of such cases. Mycoplasmas and bacteria are inconsistently present. Lesions of a similar nature but less extensive and severe and usually without interstitial emphysema are seen in nondyspneic calves in these outbreaks.\textsuperscript{8}

**Progression of Acute Pneumonia Outbreaks**

A significant improvement in the clinical condition of nondyspneic calves in the early stages of pneumonia outbreaks may follow prompt antibiotic therapy, and such treatment will tend to limit residual lung damage. However, chronic bronchopneumonia develops where initial lung damage has been very severe, where the farmer has delayed or neglected seeking veterinary advice, and sometimes even despite veterinary therapy. As a result, extensive areas of consolidation remain in the lungs for months after the onset of the outbreak and are associated with chronic coughing, variable degrees of tachypnea and hyperpnea, loss of condition, and depressed feed conversion efficiency.\textsuperscript{6,62} Calves with chronic bronchopneumonia undergo periodic acute exacerbations of clinical signs ("flare ups"), many of which are associated with the development of severe bacterial exudative pneumonia. In the latter case, affected animals are depressed, anorexic, and often have a high fever.

**Pathologic and Microbiologic Findings in Late Stages of Acute Pneumonia Outbreaks**

Sacrifice of animals exhibiting respiratory signs for weeks or months, reveals pneumonic areas of variable extent in the anterior lung lobes. Widespread fibrosis of the walls of small airways is often appreciable grossly, and purulent exudate can be expressed from airway lumina. Fibrous adhesions may be present between adjacent lung lobes and the mediastinum.

Microscopically, the most striking changes are those causing distortion and obliteration of small airways.\textsuperscript{7,62} There is widespread organization of bronchiolar exudate by macrophages and fibroblasts which leads to occlusion of bronchiolar lumina by fibrous masses (Fig. 5). Peribronchial and peribronchiolar fibrosis also occurs, and there is a variable amount of peribronchial and peribronchiolar lymphoid hyperplasia, which, in a proportion of cases, may be sufficiently pronounced to form lymphoid "cuffs." Zones of interalveolar and interlobular fibrosis also occur. These changes are sequelae to severe bronchiolar and alveolar damage occurring in the early stages of the outbreak. They are often extensive, severe, persistent, and refractory to conventional therapy. Mycoplasmas and *Pasteurella* sp. may be recovered from the lungs at this stage, but viral antigens are usually not detectable.

**Secondary Bacterial Pneumonia**

Mortalities due to severe secondary bacterial pneumonia may occur at any stage of calf pneumonia outbreaks. Necropsy reveals marked swelling and consolidation of affected lung lobes. A mild to moderate fibrinous pleurisy is usually present, and interlobular septa may be moderately swollen. Superficially and on section, bronchioli and alveoli are outlined by greyish-yellow purulent foci; large areas of coagulative or suppurative necrosis are
Figure 5. A, Organization of bronchiolar exudate with establishment of fibrous tissue within bronchiolar lumen (H and E stain). B, Widespread bronchiolitis obliterans with fibrous masses (arrows) occluding bronchiolar lumina (H and E stain).

often visible. On sectioning, much purulent exudate can be expressed from small airways.

Microscopically, severe exudative changes are present, particularly within alveoli, where there is a marked infiltration of macrophages and neutrophils, often with formation of “oat cells.” Necrosis of interalveolar septa allows the formation of large aggregates of leukocytes. Vascular damage is marked, with thrombosis of small blood vessels and alveolar capillaries and severe alveolar edema with precipitation of proteinaceous material. Lymphatics in interlobular septa are distended and thrombosed, and there is interlobular edema. Numerous bacterial colonies are often visible in bronchiolar and alveolar lumina. Large numbers of Pasteurella, H. somnus and, on occasion, Salmonella sp. may be recovered from such lesions.7-45

Insidious Onset Chronic Pneumonia (“Cuffing Pneumonia”)

This pneumonia was first described by workers in the West of Scotland26 and has subsequently been reported in calves in Canada.13 Clinically, uncomplicated “cuffing pneumonia” is a high-morbidity, low-mortality pneumonia characterized by frequent harsh coughing, slight to moderate tachypnea, and mild hyperpnea. In some cases, rhonchi may be heard cranio-
ventrally. Although affected animals are alert and have a good appetite, their growth rate is reduced.\textsuperscript{65}

The basis of the “cuffing pneumonia” lesion is a hyperplasia of the normally small amount of peribronchiolar lymphoid tissue forming expanding lymphoid cuffs that surround and compress bronchi, bronchioli, and adjacent alveoli.

“Cuffing pneumonia” is found in the cranoventral segments of lung. The pneumatic tissue is dark red or purple, and pneumatic lobules are partially collapsed. The hyperplastic lymphoid tissue may be visible macroscopically forming greyish cuffs several millimeters in diameter that surround affected bronchi.\textsuperscript{65} As mentioned previously, a significant association has been noted between \textit{M. dispar} and “cuffing pneumonia.” However, the pathogenesis of this pneumonia is poorly described, and it is not clear whether mycoplasmas are the sole agents involved in the genesis of the lesion. “Cuffing pneumonia” may become complicated by a secondary bacterial pneumonia caused by \textit{P. multocida} or \textit{C. pyogenes}.

**DETECTION AND DIAGNOSIS OF ETIOLOGIC AGENTS IN CALF PNEUMONIA OUTBREAKS**

It is particularly important to identify primary etiologic agents in pneumonia outbreaks so that vaccines containing relevant pathogens can be developed, efficient vaccination programs can be formulated on individual farms, and new syndromes and new infections can be identified. Most pathogenic mycoplasmas and bacteria can be recovered on artificial media with relative ease from specimens taken from the upper and lower respiratory tracts of pneumatic calves. Detection of viral activity is more difficult, and it is essential that suitable specimens are submitted to the diagnostic virology and pathology laboratory. Although laboratory diagnosis of respiratory disease is covered in a separate article, some comments, particularly on the submission of specimens by the practitioner, are relevant at this point.

**Clinical Assessment**

In most pneumonia outbreaks, it is not possible to diagnose with certainty which viruses or mycoplasmas are present by clinical examination alone. Nevertheless, there may be some useful clinical pointers. Outbreaks of severe pneumonia in which there is rapid onset of severe respiratory distress in a number of calves, with necropsy findings of consolidation in the anterior lung lobes and severe interstitial emphysema, should arouse suspicion of acute RSV or RSV and PI-3 virus pneumonia. Pneumoenteritis may be observed in BVD virus, adenovirus, or coronavirus infections. Arthritis may accompany respiratory signs in which \textit{M. bovis} is involved.

Demonstration of viruses and mycoplasmas will involve sampling of the upper respiratory tract of a number of animals, submission of paired sera, and, ideally, submission of one or more animals from the outbreak for necropsy.

**Sampling the Upper Respiratory Tract for Viruses**

Virus is most likely to be detectable in nasal secretions in the acute stage of pneumonia outbreaks, so it is important to take nasal samples at an
early stage, ideally on the day acute respiratory signs are first noted. A minimum of six animals should be sampled, and a range of clinical severities should be represented. Nasal swabs, tampons, or suction apparatus may be used. Nasal swabs with nylon bristles are preferable to traditional cotton-wool swabs. A particularly satisfactory method of sampling involves the use of a portable vacuum pump that extracts a sample of nasal mucus into a small container. Epithelial cells can then be separated from the mucus sample and examined for viral antigens by immunofluorescence staining with a battery of conjugated antisera. This technique allows a rapid diagnosis of virus infection, is more sensitive than virus isolation, and is particularly suitable for the detection of viruses such as RSV or coronavirus, which are extremely difficult to isolate in cell cultures and which may be present in mixed infections with other more rapidly growing viruses. Immunofluorescence staining of nasal epithelial cells has been used in the detection of PI-3 virus, RSV, BVD/MD virus, coronavirus, and IBR virus infections of the respiratory tract (Fig. 6). It should be remembered that certain respiratory viruses, particularly RSV, are notoriously labile, and specimens should be submitted as quickly as possible to the diagnostic laboratory.

Submission of Paired Sera

The demonstration, in several animals in a group, of a fourfold or greater increase in viral antibody titer between acute and convalescent serum samples is indicative of recent infection. The acute phase sample must be taken as near as possible to the time of onset of respiratory signs, otherwise sero-
logic conversion may not be demonstrable. Convalescent samples should be taken from the same animals 3 weeks later. Submission of a single batch of sera is unsatisfactory. Serologic diagnosis alone in calves less than 4 months old is unreliable, for persisting maternal antibodies may block an active serologic response to viral infection.  

Submission of Necropsy Material

Submission of entire animals or portions of the lower respiratory tract facilitates pathologic and microbiologic examination of pneumonic lung. Where lung tissue is being taken for submission to the diagnostic laboratory a number of samples should be selected from each affected lobe, for lesions at various stages may be present in different regions of lung. Formalin-fixed blocks as well as unfixed samples should be submitted.

Histopathologic examination of lung is of particular value in the diagnosis of acute viral pneumonia associated with RSV or PI-3 virus infection and in the diagnosis of "cuffing pneumonia" and severe bacterial exudative pneumonia.

Submission of unfixed lung specimens allows cultural examination for viruses, mycoplasmas and bacteria to be carried out and also facilitates rapid diagnosis of viral and mycoplasmal infection by immunofluorescence or immunoperoxidase staining of lung impression smears or cryostat sections. Detection of viral antigen by immunofluorescent or immunoperoxidase staining of formalin-fixed paraffin sections of lung is also possible.

Unfortunately, many of the calves submitted for necropsy from pneumonia outbreaks are those that have died after a long period of respiratory illness or that have become stunted and uneconomic to keep. In many cases, therefore, lung damage will be of a chronic nature or dominated by severe bacterial exudative changes and little information may be gained either by pathologic or microbiologic examination as to which agents were responsible for initiating the problem. Sacrifice of one or more calves at the time of onset of disease should be considered in severe outbreaks of pneumonia, particularly when a large number of valuable animals are involved. Such a policy provides optimal material for pathologic and microbiologic investigation, is most likely to result in the identification of primary etiologic agents, and accelerates the development of successful therapeutic and prophylactic regimens.

Assessment of the relative contribution of viruses, mycoplasmas, and bacteria to lung damage in a particular outbreak must be made cautiously and will involve consideration of all the agents isolated or demonstrated, the nature of the damage to the lung, and the response of affected calves to antibiotic therapy.

TREATMENT

At present, effective antiviral chemotherapeutics are not commercially available for use in calf pneumonia. Therefore, treatment is based on antibiotic therapy directed against the mycoplasmal and bacterial components of the disease. Good in-vitro activity against M. dispar and bovine respiratory
tract ureaplasmas has been demonstrated for the antibiotics tiamulin hydrogen fumarate and tylosin tartrate. In severe outbreaks, it is best to treat the entire group with antibiotics administered by parenteral routes using a regimen that maintains therapeutic levels in the lung for at least 3 to 4 days. In the experience of the author, a combination of intramuscular tylosin tartrate administered at a dose rate of 10 mg per kg daily for 3 to 4 days with another broad-spectrum antibiotic such as oxytetracycline to provide additional activity against Pasteurella sp. has often produced satisfactory results. This is particularly true when the first dose of oxytetracycline has been administered intravenously at a rate of 20 mg per kg. Encouraging results have also been reported following the use of a combination of lincomycin and spectinomycin (50 mg lincomycin and 100 mg spectinomycin per ml) administered by intramuscular injection for 3 to 5 days at a rate of 15 mg per kg (1 ml per 10 kg). Antibiotic therapy is most likely to be effective when applied in the early stages of outbreaks, or to treat acute bacterial exacerbations of respiratory disease. Where viruses are not playing a major role in the production of lung damage, a satisfactory clinical response may occur over a period of 24 to 72 hours. In cases of severe viral pneumonia or cases of chronic pneumonia in which fibrous broncho-occlusive lesions or lymphoid “cuffing” lesions are well established, antibiotic therapy will have a lesser impact. Response to antibiotic therapy may also be disappointing in cases in which M. bovis is involved. Severely affected animals that fail to respond to antibiotic therapy alone are commonly treated with anti-inflammatory agents. A popular method of anti-inflammatory therapy involves the administration of one or more doses of corticosteroids (for example, one or two intravenous injections of dexamethasone at a dose rate of 20 to 40 mg per 50 kg). Corticosteroids may, on occasion, cause exacerbations of viral respiratory tract disease. A recent report has indicated the potential value of an alternative form of anti-inflammatory therapy using the antiprostaglandin compound flunixin meglumine. When this drug was given intravenously at a dose rate of 2.2 mg per kg for 3 consecutive days, it markedly reduced the severity of clinical signs and extent of pulmonary consolidation in experimental PI-3 virus pneumonia of calves.

Bronchodilators such as clenbuterol or etemiphylline and mucolytics such as bromhexine hydrochloride are also available for the treatment of calf pneumonia. When bromhexine hydrochloride is administered simultaneously with oxytetracycline, the levels of the latter in bronchial mucus are considerably increased. Unfortunately, little detailed clinical information has been published with which to assess the efficacy of bronchodilator or mucolytic therapy.

In addition to providing drug therapy, it is important to identify and, if possible, to remedy housing faults such as overstocking, poor ventilation, or drafts that may be exacerbating the respiratory problem.

**CONTROL OF CALF PNEUMONIA**

A program to prevent pneumonia on a calf-rearing unit should include measures to reduce environmental stress and avoid conditions favorable to...
the spread of infectious respiratory disease; it should also incorporate specific prophylactic measures directed against the microorganisms associated with calf pneumonia.

Housing

In housing the calf in its first few months of life, the main aim is to provide a dry and draft-free environment with adequate ventilation (minimum 34 m³ per hr per calf) and cubic air capacity (minimum 6 m³ per calf). Provision of good ventilation does not necessarily involve the installation of expensive controlled environment systems. With adequate provision and careful siting of air inlets and outlets, it may be possible to achieve effective ventilation without drafts by natural means utilizing the stack effect. For calves up to 3 months, an inlet area of 0.045 m² per calf and an outlet area of 0.04 m² per calf with the outlets placed 1.5 to 2.5 m above the inlets has been recommended. Air inlets should be situated well above the level of calf pens to avoid drafts.

Whenever possible, calves of a similar age should be reared in self-contained groups and an "all in, all out" policy adopted, thus allowing periodic depopulation and disinfection of calf houses. No more than 60 calves should be present in any one airspace. One should avoid feeding calves mouldy hay and dusty meal.

Colostrum Feeding

Antibodies to bovine respiratory viruses such as PI-3 virus and RSV are widespread in the adult cattle population, and most calves, provided they are given access to colostrum at a suitable time, will obtain maternal antibodies that may persist in serum for 3 to 4 months. The efficacy of colostral antibody against respiratory disease in the first few months of the calf's life is not clear. However, in one report of experimental PI-3 virus infection, more severe clinical signs were produced in calves deprived of colostrum than in calves fed colostrum using the same inoculation regimen. Many outbreaks of pneumonia occur at a time when maternal antibodies are waning or have disappeared; in one study, calves with total serum immunoglobulin levels in excess of 20 zinc sulphate turbidity test units (ZSTU) at 10 days of age were found to be significantly less prone to fatal and nonfatal respiratory disease during the first 5 months of life than calves with levels below 20 ZSTU. It would appear prudent, therefore, to ensure that calves are fed adequate amounts of colostrum at an early stage in life (6 pints in the first 6 hr).

Vaccination

Even under optimum housing conditions, severe outbreaks of pneumonia may still occur; therefore, it is necessary to develop effective vaccination programs. Vaccination programs on different farms will vary depending on the history of respiratory disease, the microorganisms that have been associated with the respiratory disease, and the management practices on the farm. Development of successful programs is complicated by the fact that a number of different microorganisms are capable of producing primary
pneumonia in the calf lung and that, in many instances, it will be necessary to protect a very young age group of calves.

**Vaccination Against Viruses**

The priority at present is to prevent severe lung damage caused by RSV and PI-3 virus. It is hoped that by blocking primary pneumonia caused by these viruses, the opportunity for mycoplasmas and secondary bacterial infection to inflict additional lung damage will also be reduced.

Circulation of RSV and PI-3 virus occurs nearly every year in rearing calves in dairy herds, and infections are most common in the last few months of the year. Calves born in late summer and autumn, therefore, may experience PI-3 virus or RSV-associated pneumonia in their first few months of life. In contrast, calves born in the spring and pastured during the summer may not be challenged until the following autumn and winter housing period, when they are 6 to 9 months old.

The priority in vaccinating calves born in late summer and autumn is to achieve a rapid onset of protection and to avoid or overcome interference with vaccine by maternal antibody. Theoretically, at least, these objectives are most likely to be achieved by intranasal vaccination using live vaccine. Live PI-3 vaccines designed for intranasal use are commercially available and are safe to use in young calves. For calves vaccinated when they are only a few days or a few weeks old, a booster vaccination will be necessary 4 to 8 weeks later to ensure the persistence of local antibody in nasal secretions.

In contrast, intranasal RSV vaccines are not available. The only RSV vaccine commercially available at present is a live attenuated vaccine designed for intramuscular use. A primary vaccination regimen with this product necessitates two inoculations given at least 3 weeks apart. Ideally, the vaccine is administered to seronegative animals, and following a primary vaccination regimen manufacturers claim a duration of immunity of at least 4 months.

Unfortunately, however, response to live RSV vaccine given by the intramuscular route is severely depressed by circulating maternal antibody. Also, for young calves that are being vaccinated in anticipation of a disease problem at 2 to 4 months of age, persisting maternal antibody to RSV may interfere with the "take" of the first inoculation of vaccine. In an attempt to overcome this, the manufacturers recommend an additional inoculation of vaccine when calves less than 4 months old are being vaccinated.

Calves born in the spring and pastured during the summer may not experience RSV disease until the autumn. In spring calving herds with no history of serious respiratory problems early in the year, vaccination may be delayed to the later summer period, at which time the calves will be older and maternal antibodies will have largely disappeared.

A major double-blind field trial was carried out in the Netherlands using an intramuscular live attenuated RSV vaccine derived from a European strain of RSV.* The trial involved 530 calves that were 2 to 10 months of age at the time of their first vaccination. Vaccination was carried out at 27 dairy

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*Rispoval. Smith Kline & French Laboratories, Philadelphia, Pennsylvania.
farms where respiratory problems due to RSV had been observed during the preceding year. In completely vaccinated groups, the incidence of RSV infection and the incidence of lower respiratory tract disease due to RSV was significantly reduced compared to unvaccinated groups. Generally, only mild signs of upper respiratory tract disease were present in completely vaccinated groups following RSV infection.61

In a recent study, an experimental inactivated RSV vaccine was compared with two live vaccines in a group of calves aged 4 to 8 months.50 These calves had low or undetectable levels of maternal antibody to RSV. The inactivated vaccine consisted of glutaraldehyde-fixed bovine nasal mucosa cells persistently infected with RSV and emulsified with oil adjuvant and was administered subcutaneously. The live vaccines were (1) a modified live virus vaccine derived from a bovine strain of RSV and (2) a temperature-sensitive vaccine derived from a human strain of RSV. Both live vaccines were administered intramuscularly. Following experimental intranasal challenge with RSV 2 weeks after vaccination, 11 out of 12 calves vaccinated with the inactivated vaccine were found to be completely protected against RSV infection. The two live vaccines did not confer protection against infection, although they did reduce virus shedding. The challenge virus did not induce disease in control animals.

RSV vaccine has become available only recently, and it will be some time before the impact of vaccination programs using currently available PI-3 virus and RSV vaccines on calf pneumonia can be assessed. To overcome the problem of colostral antibody interference in young calves, it may be necessary to develop live intranasal or inactivated RSV vaccines. The preliminary results mentioned previously for an inactivated RSV vaccine based on glutaraldehyde-fixed cells are particularly encouraging. Further trials are necessary, however, and this vaccine is not yet commercially available. Future epidemiologic and pathogenetic studies may reveal that it is necessary to increase the spectrum of virus vaccines in the prophylaxis of calf pneumonia to include such agents as BVD virus, adenoviruses, or some of the more recently recognized respiratory virus infections, such as calf coronavirus.

Vaccination Against Mycoplasmas

Even allowing for successful immunoprophylaxis of viral respiratory disease, it should also be remembered that M. bovis, M. dispar, and ureaplasmas have also been shown to be capable of producing primary pneumonia in the calf, albeit of limited extent and clinical severity. In order to achieve complete control of calf pneumonia, mycoplasma vaccines may also have to be used. Although these are not commercially available at present, experimental M. bovis and M. dispar vaccines have been produced. These consisted of formalin-killed organisms and oil adjuvant and conferred protection against experimental challenge with M. bovis and M. dispar.23,24

Vaccination Against Bacteria

The majority of bacteria in calf pneumonia, including Pasteurella sp. and C. pyogenes appear to act mainly as secondary invaders. Hopefully, if primary viral and mycoplasmal damage in the lungs could be abolished, the
effect of these would be neutralized. However, in incidents in which *H. somnus* is associated with pneumonia, vaccination may have to be considered, for *H. somnus* is capable of acting as a significant primary lung pathogen.

**Prophylactic Use of Antibiotics**

Oral administration of antibiotics such as tylosin tartrate or tetracyclines has been used as a prophylactic measure in calf pneumonia.\(^{33,34}\) This has reduced the clinical severity, mortality rates, and incidence of severe lung lesions in certain instances. This is a most unsatisfactory method of prophylaxis for the following reasons: Firstly, antibiotics will not prevent viral respiratory tract damage. Secondly, although the frequency of isolation of *Mycoplasma* sp. and *P. multocida* is reduced, infection has not been eliminated from the respiratory tract and lung lesions have not been prevented. Thirdly, the long-term oral administration of antibiotics will facilitate the emergence of antibiotic-resistant bacteria and is likely to interfere with the development of a normal ruminal bacterial flora.

**Paraimmunity Inducers and Bovine Interferon**

The use of interferon inducers or the direct use of bovine interferon as a tool in the prophylaxis or treatment of calf pneumonia is an interesting possibility for the future. However, much in vitro and in vivo research is required before the full potential of this approach can be assessed.

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