Understanding the mechanism of metaphylaxis from an epidemiologic perspective

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Abstract

Metaphylaxis has become an integral component of BRD control in high-risk cattle in North America. It has proven to be both effective and economically advantageous in clinical trials and in field application. The efficacy of metaphylaxis against BRD not only lies in its ability to treat cases in progress at the time of administration, but also in that metaphylaxis modifies epidemic parameters that ultimately reduce the size and severity of disease outbreaks in groups of cattle. One possible explanation for this effect is that metaphylaxis temporarily creates a uniform shift in the susceptibility of treated cattle that delays clinical disease while allowing stress to dissipate and adaptive immunity against BRD pathogens to develop. This shift, and the changes that occur while it is in effect, starve the epidemic of new susceptible cases which reduces BRD morbidity in the population. Provided this theory is accurate, metaphylaxis could be better targeted by using diagnostics to identify and treat only susceptible cattle rather than all of them; however, current technology prevents timely application of such information.

Key words: bovine respiratory disease, BRD, metaphylaxis, epidemiology

Résumé

La métaphylaxie est devenue une composante intégrale du contrôle du complexe respiratoire bovin (CRB) chez les bovins à haut risque en Amérique du Nord. Elle s'est révélée à la fois performante et avantageusement économique dans des essais cliniques et des applications sur le terrain. L'efficacité de la métaphylaxie dans le contrôle du CRB ne dépend pas seulement de sa capacité à traiter les cas courants au moment de l'administration car elle peut aussi modifier les paramètres épidémiologiques qui vont ultimement réduire la grandeur et la sévérité des flambées de la maladie dans des groupes de bovins. Une explication possible de ces effets serait que la métaphylaxie engendre temporairement une modification uniforme de la susceptibilité des bovins traités qui retarde la maladie clinique tout en permettant au stress de se dissiper et à l'immunité acquise contre les pathogènes du CRB de se développer. Cette modification de même que les changements qui surviennent quand son effet est en vigueur, réduit le nombre de nouveaux cas susceptibles nourrissant l'épidémie réduisant ainsi la morbidité reliée au CRB dans la population. Si cette théorie est correcte, la métaphylaxie pourrait être mieux ciblée en utilisant le diagnostic pour identifier et traiter seulement les bovins susceptibles plutôt que l'ensemble du groupe. Toutefois, la technologie actuelle empêche l'application opportune de cette information.

Introduction

Metaphylaxis has become an integral component of bovine respiratory disease (BRD) management in North American beef production systems (NAHMS Feedlot 2011). Clinical trials have consistently associated both health and economic advantages with metaphylactic antibiotic use in cattle of various BRD risk categories, and especially in cattle considered at high risk of developing BRD.[1,2] The efficacy of metaphylaxis is mechanistically rooted in the deleterious effect of antibiotics on pathogenic bacterial populations; however, the consistently positive outcomes of metaphylaxis are also likely to come from changes made in the dynamics of BRD epidemics. One possible explanation and the working hypothesis of these proceedings is that metaphylaxis causes a uniform, temporary reduction in susceptibility while alleviation of stress and development of acquired immunity progress. The objective of these proceedings is to discuss this hypothesis and assess its validity.

Characteristics of an Epidemic

The circumstances that set the stage for disease epidemics are well described. For any particular infectious disease, populations contain individuals that are in 1 of 3 categories: susceptible, infected/infectious, and resolved/recovered.[4] The relative proportions of individuals in each of these categories define the epidemic potential in a population. The rate at which individuals move from the susceptible category to the infected/infectious category is quantified by the reproductive ratio of the disease and depends on the infectiousness of the pathogen, the degree of effective contact needed for transmission, the duration of infection, and the presence of new susceptible hosts. In theory, a highly infectious pathogen that invades a dense population of susceptible hosts and causes a relatively long period of infection (pathogen shedding) will result in a dramatic epidemic of disease. In cases where infectivity is reduced, contact is interrupted, or few susceptible hosts are present, epidemics usually progress more slowly and last longer.

Features of Bovine Respiratory Disease Epidemics

Many viruses and bacteria have been isolated from cases of bovine respiratory disease. Many of the same bacteria associated with fatal BRD cases can be routinely isolated from the nasopharynx of healthy cattle.[5] Stress is thought to be a necessary component in the pathogenesis of BRD epidemics in groups of cattle. Factors such as abrupt weaning, castration, transport, commingling, environmental change, nutritional changes, and weather events have been implicated as important stressors contributing to the development of BRD.[3]

Cattle at high risk of developing BRD are categorized at that risk level because they have experienced many of the stressors that drive BRD, and they are typically naïve to many or all of the BRD pathogens. Enough individuals in accumulated groups are infected with these pathogens to initiate BRD epidemics as transmission from 1 individual to another or from the nasopharynx to the lungs begins to occur. This transmission is thought to be facilitated by commingling and close contact associated with transport.

The Role of Metaphylaxis in BRD Epidemics

The use of metaphylaxis appears to have a greater role than simply treating cases of BRD that are already in progress when the metaphylactic treatment is applied. In other words, the epidemic is not simply delayed, but a reduction in overall BRD morbidity is observed.[1] One explanation for this reduction is that metaphylaxis changes the dynamics of the epidemic in its early stages. Assuming that the pathogenic bacteria present in the population are sensitive to the chosen metaphylactic drug, treatment of the entire population simultaneously would temporarily shift the population from susceptible or infected to resolved. This temporary resolution lasts as long as the antibiotic is present at therapeutic levels and as long as the bacteria remain sensitive. While the early stages of an outbreak are temporarily contained by the presence of the metaphylactic antibiotic, calves begin to dissipate stress accumulated during marketing and begin building immunity to recently acquired pathogens. By the time metaphylaxis wanes, some calves have developed enough immunity to remain clinically healthy and avoid a return to susceptible/infected status. Other calves, due to ongoing stress or overwhelming challenge, return to susceptible status and develop clinical disease requiring further treatment.

If this theory has merit, metaphylaxis functions epidemiologically as a modifier of the disease reproduction factor (R_0) by forcing a temporary change in the susceptible population while allowing continued progress toward permanent shifts of susceptible cattle to the resolved category. An epidemic can be thought of as a fire. Early on, a fire starts small and has relatively little impact, but in the presence of an ample supply of fuel the fire will quickly burn out of control. The epidemiologic function of metaphylaxis is comparable to suppressing the fire long enough to provide time to remove most of the fuel. The initial protection from mass treatment does not extinguish the epidemic, but rather arrests it temporarily while the cattle adapt to their new environment and begin to build adaptive immune responses to their newly acquired complement of infections. As calves develop adequate immunity to prevent clinical disease in the absence of antibiotic, they are removed from the supply of "fuel" for the BRD epidemic "fire." Since the R_0 is dependent on the number of susceptible individuals in a population, a reduction in susceptible individuals will reduce the rate of accumulation of new cases, thereby slowing and eventually stopping the epidemic as it runs out of fuel. This mechanism may explain part of why BRD morbidity is reduced in metaphylacticly treated groups of cattle rather than simply having the outbreak delayed by the duration of the antibiotic used.

If this theory is driving the decrease in BRD morbidity, some assumptions would have to be valid. First, calves would have to be assumed to already be incubating pathogens, and in particular, pathogenic bacteria. If metaphylaxis were applied prior to acquisition of the pathogenic bacteria, infection would likely be prevented in many individuals and those animals would return to a fully susceptible state following loss of therapeutic antibiotic levels. Second, to achieve the most robust effect, all susceptible individuals in a population would need to be treated. If this assumption were not true, continued susceptibility heterogeneity in the population of cattle would allow the epidemic to grow in the cattle not protected by antibiotics and allow amplification of pathogenic load in the population that would have the potential to overcome relatively immature acquired immunity in the protected calves. This set of circumstances may allow a BRD epidemic to progress relatively unchecked in a population. Third, the population is assumed to be stable. If individuals continue to flow in and out of a population, the epidemic will be fueled by the arrival of new susceptible individuals and the loss of resolved, immune individuals that effectively serve as fire breaks for remaining susceptible individuals.

The Role of Diagnostics in Metaphylaxis

The use of diagnostics related to BRD-targeted antibiotic use remains limited. Decision making related to antibiotic application, including choice of antibiotics, timing, and selection of individuals or groups to treat typically must be completed at a pace incompatible with the speed of current diagnostic modalities. As a result, discussion of diagnostic use in BRD centers around what tools would be useful in enhancing the efficacy and value of antibiotic use. This is particularly true for metaphylaxis, as the decision to use metaphylactic antibiotics is made and executed very shortly after the arrival of newly purchased cattle. Diagnostics could help enhance the value of metaphylaxis by matching antibiotics to the existing complement of bacteria existing in a population based on spectrum and antibiotic resistance. Diagnostics could

also help characterize the BRD risk of both populations and individuals within those populations.

Conclusions

The theory of the epidemiologic function of metaphylaxis essentially positions it as a biocontainment tool. As the circumstances related to antibiotic use continue to change, particularly in the areas of social acceptance and regulation, more pressure is likely to be placed on strategies that limit antibiotic use to avoid development of resistance. If metaphylaxis is indeed a biocontainment tool that modifies epidemic dynamics, improved used of metaphylaxis can be achieved by thoroughly understanding the mechanisms by which these modifications occur. Further, if tools to target metaphylaxis to the susceptible animals at the speed of current production can be developed, little loss in efficacy and a reduction in total antibiotic use can be expected. In the event that metaphylaxis is no longer allowed in cattle production, understanding BRD epidemics may offer other techniques that can be used to elicit similar outcomes without the need for antibiotics.

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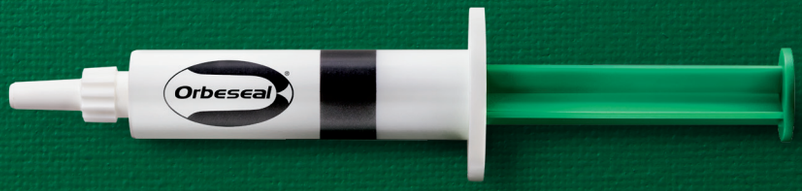

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