

Chinese Medicine in the Treatment of Suspected Neonatal Septicemia in Two Bull Calves

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Abbreviations

EPF	External Pathogenic Factor
TCVM	Traditional Chinese Veterinary Medicine
CCM	Classical Chinese Medicine

Abstract

Two neonatal beef calves diagnosed clinically with acute septicemia were treated with a combination of 2 Chinese herbal formulas, *Gao Mao Ling* and *Huo Xiang Zheng Qi San*. The responses were dramatic, with complete recoveries in 5 days. The rapid responses were correlated with the administration of the herbal formulas, which had been prescribed based on the Chinese philosophical understanding of disease progression.

Introduction

Sepsis is the number one cause of neonatal foal and calf mortality, with survival rates typically less than 12% (1). It is broadly defined as an overwhelming systemic inflammatory response syndrome (SIRS) triggered by infectious organisms. Bacteria such as *Escherichia coli*, *Listeria monocytogenes*, *Pasteurella* spp, *Streptococcus* spp, *Salmonella* spp, *Clostridium perfringens*, *Campylobacter* spp, *Klebsiella* spp, and different *Staphylococcus* species can be involved (2, 3). Septicemia is characterized by alterations of temperature regulation, hypo- or hyperthermia with fluctuations, in which the inflammatory cytokine cascade is initiated as part of that response and can lead to multiple organ dysfunction syndrome. Increased endothelial permeability, myocardial depression, and intermediary metabolism disruption are notable recognized complications that may result in hypovolemia, hypotension, and respiratory failure (2). Calves that fail to absorb an adequate

amount of gamma immunoglobulins (IgGs) from consumption of colostrum are the most susceptible to septicemia. If the invading bacteria are not rapidly controlled, focal infections can ensue, such as in growth plates, joints, or meninges, and generalized sepsis may occur (4). A definitive diagnosis is often difficult as it requires blood cultures. In one study, *E coli* (30.6%) was the most frequent isolate, demonstrating multidrug resistance in 90.9% of cases (5). In Chinese Medicine these bacteria would be considered as an External Pathogenic Factor (EPF), a foreign substance toxic to the body.

Hematologic changes and clinical signs vary with the severity of the disease. Early signs are nonspecific and can vary from mild depression with a weak sucking reflex to coma, and from hyperthermia to hypothermia. Advanced signs include hyperemia of mucous membranes, tachycardia, tachypnea, and a progression to hypotensive shock. Abnormal neutrophil counts (neutrophilia or neutropenia) and abnormal neutrophil morphology (bands, myelocytes, metamyelocytes) are frequently observed. Vacuolation, toxic granulation, and Döhle bodies may be present in neutrophils. The fibrinogen concentration is frequently elevated. Thrombocytopenia may develop in severe cases. Hypoglycemia or less often hyperglycemia may be observed. Organ function is compromised in severe cases, and laboratory results reflect the insufficiency (2). Conventional treatment typically involves indicated antimicrobials (prohibited for an animal to remain

certified as organic), NSAIDs, fluids, and plasma therapy (2). If not successfully treated, sepsis can lead to multiple organ dysfunction syndromes, septic shock, and death (4). Long term sequelae such as navel, hepatic, or pulmonary abscesses, and/or septic arthritis often develop (5).

Classical Chinese Medicine (CCM) has studied disease progression for over 2000 years. In CCM classical and traditional philosophy, sepsis occurs when *Wei Qi* is unable to defend against Pathogenic *Qi*, and the Pathogen invades. Due to the deficient state of the innate immune system of newborns, the pathogenic *Qi* has the potential to reach the deepest levels and layers of the body, eventually separating *Yin* and *Yang*, causing death. The calf's initial *Wei Qi* is colostrum. Zhong Zhang Ji studied the proper treatment to use when an external pathogen invades; that is, how to effectively enable the body to expel the pathogen and prevent disease suppression. He wrote the text of the *Shang Han Lun* (*On Cold Damage* in English), one of the most revered of China's traditional medical texts. This work describes, in a CCM paradigm, the proper multifaceted, multilinear treatment of disease in the face of a Cold pathogen invasion. The protocols address both the initial treatment of signs as well as strategies to use when the disease has already progressed into the deeper layers in the body. It gives the clinician tools to enable the body to successfully expel the pathogen (7). The above-referenced layers are described in the *Shang Han Lun* as 6 depths found in the body. The most exterior layers are the 3 *Yang* layers, the *Tai Yang*, *Shao Yang*, and *Yang Ming*; and the more interior *Yin* layers are the *Tai Yin*, *Shao Yin*, and *Jue Yin*. Most EPFs invade at the outermost *Tai Yang* layer, which in CCM is the purview of the Bladder and Small Intestine. If not stopped there, the disease pathogen can descend into either the *Yang Ming* (Stomach and Large Intestine), the *Shao Yang* (Triple Heater and Pericardium), or the deeper interior layers such as the *Tai Yin* (Lung and Spleen).

As clinical experience expanded over the centuries, it was recognized that not all symptoms and pathogens could be considered Cold in nature. Some infections were felt to have an initial Warm nature. These responded well to an alternative approach, described in the book *Warm Disease Theory* (*Wen Bing Xue*). This most modern of the Chinese Classical theories describes a mode and pattern of disease progression from the exterior of the body to the interior, caused by a Warm pathogen. The *Wen Bing* explanation of disease progression recognizes the complication of another Pathogenic Factor that may arise from either external or internal sources, called Dampness (8). Dampness refers to a fluid metabolism defect or disruption that results in fluid

accumulation in the tissues. *Wen Bing* theory describes the levels in the body as being the *Wei*, the most superficial immune system level, the *Qi*, organ level, the *Ying*, related to the plasma, and the *Xue*, or Blood level. These classical medical works can be of great value in the study of disease progression from an external invading pathogen. They give the practitioner a strategy to assist the animal in the expulsion of the EPF with no lingering complications.

Given the high mortality rate, concerns for antimicrobial resistance, and organic certification considerations, diagnostic insights from veterinary Traditional Chinese Medicine (TCVM) were used to prescribe Chinese herbal formulas for the treatment of presumed neonatal septicemia in 2 calves.

Case Reports

Case 1:

On a certified organic beef farm with traditional stanchioned barn layout, a Hereford bull calf was born in a manure-filled gutter. It was several hours before the owner could help the calf get up, dry off, and nurse. As the cow was in a stanchion, she was unable to assist her calf. The next day the calf was barely conscious, recumbent, and unable to rise. Upon auscultation, the lungs were very heavy-sounding, with crackling and wheezing, a pleural friction rub, and a respiratory rate greater than 140 breaths per minute. The calf's body temperature measured 40° C (104° F), and the eyes demonstrated severely injected sclerae. The ears were hot to the touch and the tongue was very wet but cold. The mucous membranes were injected and very red, and the pulse was greater than 220 beats per minute, bounding, and slippery. The calf had a swollen, still wet umbilical cord. A presumptive diagnosis of septicemia was made. The route of entry could have been oral ingestion immediately upon birth or through his umbilical area. On the basis of the TCVM evaluation of signs, a pattern diagnosis was determined to be an invasion of an EPF of Cold/Damp into the *Tai Yin* layer (Lung clinical signs), with resulting stagnant *Qi*, creating Heat in the *Yang Ming* layer (fever, red mucous membranes), with an additional possible primary Heat Toxin present. Heat Toxin is a more severe manifestation of Heat, invading not only the *Wei* level but also the deeper *Qi* level (rapid pulse, hot ears, injected sclerae) with Dampness complications (wheezing respiration, pleural friction sounds, Misting of the Mind).

The calf was moved to a box stall with the cow, and although the owner was attempting to keep him dry and clean, his umbilical cord was still wet and swollen. Given that his

mother was very protective, the acupuncture technique was fast, using LI-4, LI-11, tip of ear and tail, and BL-40, with a total of 3 mL of selenium-vitamin E emulsion (1mg Se/mL) (Bo-Se; Merck) for aquapuncture. The soil in western New York State is deficient in selenium, so treating with this mineral is routine for all newborns. The calf was prescribed 2 patent Chinese herbal formulas in tincture form: *Gan Mao Ling* (Kan Herb Company) and Early Comfort, a tincture of *Huo Xiang Zheng Qi San* (Kan Herb Company) at a dose of 60 drops of each, PO. The navel was dipped with a commercial iodine-based product, Supra-7 (from Central Tractor, now closed). Within an hour after receiving the herbal tinctures, the calf arose and nursed. His body temperature was 39.4° C (103° F), and his respiration rate had decreased to 100 breaths per minute. The following day, respiration was 80 breaths per minute, wheezing was less audible, and no pleural friction sounds were noted. Mucous membranes were pink, and decreased scleral injection was evident. The calf continued to do well with continued dosage of 60 drops of each tincture 4 times a day for the next 5 days. At this time, temperature was 38.9° C (102° F), respiration rate was 50 breaths per minute, mucous membranes were pink, there appeared to be no scleral injection, and the umbilical area was dry with no swelling. The herbal formulas were decreased to BID. Five days later, the calf appeared normal on physical examination. Respiration rate was 40 breaths per minute, body temperature remained 38.9° C, and no abnormal lung sounds were heard. Due to the resolution of the identified TCVM patterns, both herbal formulas were discontinued. On subsequent farm visits, the bull calf was seen in the pasture with his dam, with no complaints from the owner.

Case 2:

A second Hereford bull calf was born on the same farm as in Case 1. Although he was born in a bedded box stall with an attentive mother, the caretaker (with the owner out of town) was not able to dip his navel. Two days later, the calf was noted to be breathing heavily with 140 breaths per minute, and lung auscultation revealed very heavy moist rales and wheezing with pleural friction rub. The calf was nursing slowly, had a body temperature of 39.7° C (103.5° F), and a rapid, bounding, slippery pulse of over 200 beats per minute. Phlegm was visible on the tongue, and the mucous membranes were red. The TCVM diagnosis was invasion of an EPF of Cold/Damp to the *Tai Yin* layer, stagnating *Qi* and creating Heat in the *Yang Ming* layer. Similar to the first case, these signs could also be associated with a possible primary Heat toxin invading not only the *Wei* level but also the *Qi* level with Dampness complications. The initial treatment for this calf was also *Gan Mao Ling* and *Huo Xiang Zheng Qi San*, 60 drops PO of each. Within 24 hours he

appeared normal with a normal respiration rate. His mother was extremely protective, allowing no human contact, so no followup physical examinations could be performed. Because continued direct administration of herbs to the calf was not possible, subsequent doses were given instead to the cow—80 drops of each tincture in a small amount of grain BID—with the intent of passing the herbal actions through the milk. In 7 days, the calf displayed a normal respiration rate and vigorous nursing behaviors, so the herbal tinctures were discontinued. During subsequent farm visits, he was seen in the pasture with his dam, in apparent good health.

Discussion

Four criteria are necessary to establish a diagnosis of septicemia: a positive blood culture, abnormal core temperature, heart rate abnormality (tachycardia or bradycardia) with associated tachypnea, and leukocyte count abnormality (leucopenia or leukocytosis). Although hematological testing was not performed, the clinical signs for each calf justified a presumed diagnosis of neonatal septicemia. The most frequent isolate in blood cultures is *E coli* (30.6%), of which 90.9% are multidrug resistant (5). Immediate treatment is critical to save these animals. Since this was an organic farm, a non-antibiotic treatment was preferred. Due to prevailing farm economics, blood cultures and immediate blood work were declined by the owner.

Chinese Medicine recognizes disease as patterns, not via specific organisms. Bacteria such as *E coli* and others identified in calf neonatal septicemia, viral organisms such as those causing infectious bovine rhinotracheitis and bovine viral diarrhea, and rotaviruses all would be classified in TCVM as an EPF such as Heat, Cold, Dampness, or Wind. Both calves in this report were invaded by an EPF, with resulting *Qi* stagnation creating Heat and interior Dampness. Physiologic assistance was required to expel the EPF and to eliminate the interior Dampness and turbidity (thickened dampness). It was felt that the EPFs in both cases had progressed deeper than the *Wei* level and were affecting the *Qi* level with signs of Heat. The initial EPF could have been either Heat, *E coli*, Cold/Damp, or the microbial bouquet in the environment of the gutter, which then invaded directly into the *Tai Yin* layer, which is one of the more interiorly located layers, affecting the Lung and Spleen. In Chinese physiology, the Spleen produces the *Wei Qi*, comparable to the innate immune system. The treatment goal is to clear Heat at the *Wei* level and clear Dampness accumulating in the *Tai Yin* and *Qi* level (characterized in this instance by moist wheezing rales with pleural friction sounds). Basically, the goal is to reverse the inflammatory septic cascade.

Gan Mao Ling is a formula that addresses External Wind-Heat patterns and is designed to clear Exterior Heat, with any secondary Wind (tremors, muscular spasms, etc.) and Heat at the *Wei* and *Qi* level (9). It dispels EPFs from the surface layer of the body while trying to prevent invasion into the deeper internal layers. The primary herb which focuses the formula's effect is pubescent holly root, *Mao Dong Qing*, which invigorates Blood and clears Heat. Studies illustrate the immunoregulatory effect of *Mao Dong Qing* and the methods by which this herb can help control the sepsis. Research in vivo has shown there to be anti-inflammatory and analgesic effects, with the suggestion that the molecular mechanisms might be associated with inhibition of elevated expression of cyclooxygenase-2 (COX-2) protein and the overproduction of pro-inflammatory cytokines, as well as augmentation of the anti-inflammatory cytokines interleukin-4 and interleukin-10 (10). Interestingly, when *Mao Dong Qing* is administered orally in a TCM extract form, the tincture displays unique enhanced intestinal absorption characteristics. In other words, the effect when using the whole herb is much greater than what is achievable using any isolated component of the herb, reflecting the holistic benefits to using traditional Chinese medicines. *Evodia lepta* leaf and root (*San Cha Ku* in pinyin), one of the assistant herbs in *Gan Mao Ling*, clears Heat and Fire invasion. *Evodia's* effects are partly due to its suppression of Src-family and Syk tyrosine kinases and nuclear factor kappa B (11). *Isatis* root (*Ban Lan Gen*), another assistant herb, drains Heat, clears Fire, cools the Blood, and benefits the throat. Constituents found in *isatis* root have shown antiviral activity in severe acute respiratory syndrome (SARS), cytomegalovirus infections, dengue, and influenza infections, and antibacterial activity against hemolytic streptococci, *Shigella dysenteriae*, *Helicobacter pylori*, *Clostridium difficile*, and salmonellae-based enteritis (11, 12).

Chrysanthemum flower (*Ju Hua*), another herb in the formula, dispels Wind, clears Heat, and calms the Liver. *Ju Hua* has been shown to have in vitro antibacterial activity against *Staphylococcus*, *Bacillus dysenteriae*, *E coli*, *Streptococcus*, and methicillin-resistant *Staphylococcus aureus* (11). Simple-leaf chaste tree fruit, *Man Jing Zi*, clears externally-contracted Wind Heat. Honeysuckle flower, *Jin Yin Hua*, clears Heat and Fire invasions and disperses externally-contracted Wind Heat (11). With the advent of COVID-19, massive amounts of research have been conducted with honeysuckle. It has been shown that *Jin Yin Hua* works by activating the host defense system as well as directly inhibiting virus proliferation by targeting viral proteins. In an animal study, honeysuckle (*Lonicera japonica*) was found to contain a constituent (MIR2911, a

microRNA) that targets influenza A virus replication. Its active compounds were highly stable in decoctions and specifically inhibited H1N1, H5N1, and H7N9 influenza virus strains (13).

Huo Xiang Zheng Qi San is a formula indicated for acute viral or bacterial gastroenteritis (14). It is best suited for treating Exterior syndromes accompanied by internal Dampness. The leading, or *king*, herb in the formula is Chinese giant hyssop, *Huo Xiang*. This herb is felt to release Exterior Wind-Cold and dispel Dampness, enabling the clear *Qi* to ascend and turbid *Qi* to descend. Additional herbal components perilla leaf, *Zi Su Ye*, and *Angelica dahurica*, *Bai Zhi*, release the Exterior Wind-Cold and dispel Interior Dampness and turbidity. *Bai Zhi* is another herb that has illustrated a modulating effect on the immune response in cases of sepsis, strongly inhibiting airway inflammation, mucus production, and inflammatory markers such as cytokines and IgE (11). Processed pinella, *Ban Xia Qu*, and tangerine or orange rind, *Chen Pi*, transform Dampness, harmonize the Stomach, and redirect the reversed flow of *Qi*. In an animal study, the combination of *Ban Xia* and *Chen Pi* inhibited eosinophil infiltration and airway hyper-responsiveness by reducing histamine and Th-2 cytokine production in an asthma model. *Atractylodes*, *Bai Zhu*, and *poria*, *Fu Ling*, strengthen the Spleen, dispel Dampness, and harmonize the middle *Jiao*. In laboratory studies, *Bai Zhu* extract increased healing of intestinal epithelial tissue, and a polysaccharide extract of *Bai Zhu* enhanced the growth of healthy gut flora (11). *Bai Zhu* is used in herbal cancer protocols to control HIV-induced diarrhea and to inhibit cachexia caused by cancer. *Magnolia* bark, *Hou Po*, and betel husk, *Da Fu Pi*, activate *Qi* and dispel Dampness. Betel husk has been shown to influence the GI system; it strengthens the contractions and tone of the intestines. *Platycodon*, *Jie Geng*, ventilates the lung and resolves Dampness. *Jie Geng* has a Lung/Large Intestine connection, making it helpful in treating lung infections with excessive mucus (Heat or Cold conditions), bronchitis, pneumonia, and chest colds. It is also antispasmodic and therefore beneficial to the bowels. *Jie Geng* is an effective tool in the treatment of pulmonary abscesses, spasmodic coughs, asthma (especially Damp asthma), and sore throats caused by Heat or Wind/Heat. This herb is also a component in formulas used for diarrhea, inflammatory bowel syndrome, rectal spasms, and intestinal abscesses. The remaining herbal constituents of *Huo Xiang Zheng Qi San*, ginger (*Sheng Jiang*), jujube (*Da Zao*), and honey roasted licorice (*Zhi Gan Cao*) regulate the Spleen and Stomach and harmonize the formula.

The combination of these 2 herbal formulas given to the calves in this report cleared the signs of accumulated Heat

Toxins, as indicated by the reduction of elevated temperature, scleral injection, and rapid pulse. Improvements in wheezing, bronchial rales, and pleural friction sounds in the lungs suggest removal of Internal Dampness. Also resolved was the comatose behavior seen in the first case, explained in TCVM as “Phlegm Obstructing the Mind.” Phlegm is a Pathogenic Factor which can arise from Heat, Fire, and Dampness blocking awareness. The calves responded rapidly, and since no antimicrobial drug was used, they did not lose their organic status. If antibiotics are required, the organic consideration is lost, and when sold, the calves are much less valuable. Neither patient developed any long-term complications from their shaky start: no navel-ill, joint-ill, pulmonary, or liver abscesses developed. Both achieved a normal market weight (454 kg [1000 pounds]) and were sold 38 months later. As conventional antimicrobial therapy would not have been the first choice on an organic farm, these cases illustrate the effectiveness of well-prescribed botanical medicines. The herbal formulas effectively cleared the external pathogens with no obstacles from drug resistance and with no long-term complications from early septic infections.

Using a deeper understanding of disease progression, the calves were treated with herbal formulas specifically designed for the pathogenic invasion. The use of alcohol tinctures allowed the formulas to be absorbed directly through mucous membranes, achieving a rapid effect. The information contained in these classical Chinese philosophies allows the practitioner to prevent deeper disease development.

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