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Treatments of clinical mastitis occurring in cows on 51 large dairy herds in Wisconsin

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ABSTRACT

Antimicrobials are frequently used for treatment of bovine mastitis and few studies have examined modern treatment strategies on large US dairy farms. The objective of this study was to describe treatment practices for clinical mastitis occurring in cows on large dairy herds in Wisconsin. Treatments performed on 747 cows experiencing cases of mild, moderate, or severe symptoms of clinical mastitis were recorded on 51 Wisconsin dairy farms. Duplicate milk samples were collected from the affected quarter for microbiological analysis at the onset of clinical mastitis and 14 to 21 d after treatment ended. Cows were treated according to individual farm protocol. Drugs and doses used for treatments were recorded for each case. Among all herds, 5 intramammary (IMM) antimicrobials (amoxicillin, hetacillin, pirlimycin, ceftiofur, and cephapirin) were used to treat cows for clinical mastitis. Of 712 cows with complete treatment data, 71.6% were treated with IMM ceftiofur either solely or combined with other antimicrobials (administered either IMM or systemically). Of cows experiencing severe symptoms of clinical mastitis, 43.8% received IMM treatment concurrent with systemic antimicrobials. Of all cows treated, 23.1% received an additional secondary treatment (either IMM, systemic, or both) because of perceived lack of response to the initial treatment. The majority of IMM treatments were administered to cows with a microbiological diagnosis of no growth (34.9%) or *Escherichia coli* (27.2%). Half of the cows experiencing cases caused by *E. coli* were treated using systemic antimicrobials in contrast to only 6.8% of cows experiencing cases caused by coagulase-negative staphylococci. In conflict with FDA regulations, which do not allow extra-label treatments using sulfonamides, a total of 22 cows from 8 farms were treated with systemic sulfadimethoxine either solely or in combination with oxytetracycline. Antimicrobial drugs were used on all herds and many cows received extra-label treatments. Great opportunity exists to improve mastitis therapy on large dairy herds, but use of more diagnostic methodologies is necessary to guide treatments. Farmers and veterinarians should work together to create protocols based on the herd needs considering reduced inappropriate and excessive use of antimicrobials.

Key words: dairy, mastitis, antimicrobial, treatment

INTRODUCTION

Mastitis is one of the most common diseases of dairy cows and is a frequent reason that cows are permanently removed from dairy production (USDA, 2009). Mastitis has significant economic effect on dairy farms, including reduced milk yield (Seegers et al., 2003; Gröhn et al., 2004), loss of milk quality premiums, increased production costs, reduced reproductive performance (Barker et al., 1998), cost of treatments (Pinzón-Sánchez et al., 2011), discarded milk, and transmission of infections to other animals (Halasa et al., 2007). In addition, treatment of mastitis accounts for the majority of antimicrobials that are administered to dairy cows (Pol and Ruegg, 2007b; USDA, 2007; Saini et al., 2012). In the United States, no antimicrobials are approved for systemic treatment of mastitis, and only a few antimicrobial drugs are labeled for intramammary (**IMM**) treatment of mastitis (Oliveira, 2012). Whereas several products have been withdrawn from the US market, no new antimicrobials have been approved for mastitis therapy since 2006. Only 2 antimicrobial classes are represented among commercially available IMM products that are approved by the US Food and Drug Administration (**FDA**). Those classes include 6 or 7 commercially available IMM products that contain β-lactams (amoxicillin, ceftiofur, cephapirin, cloxicillin, hetacillin, and penicillin) and 1 product that contains a lincosamide (pirlimycin). Many larger US farms have controlled contagious mastitis pathogens (Makovec and Ruegg, 2003), and the distribution of etiologies for clinical mastitis has shifted to a more diverse group of gram-negative and gram-positive opportunistic organisms (Smith et al., 1985; Oliveira et al., 2013). As a result, many of the available IMM drugs have limited application for treatment of many pathogens recovered

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from cases of mastitis (Wagner and Erskine, 2009). Mastitis caused by some pathogens, such as *Mycoplasma bovis*, *Prototheca* spp., *Pseudomonas* spp., *Serratia* spp., yeasts, and others, are unlikely to respond to antimicrobial therapy (Wagner and Erskine, 2009). Most farmers treat clinical mastitis based on symptoms and without microbiological analysis, thus treatments are often given regardless of etiology (Hoe and Ruegg, 2006). This strategy often results in administration of antimicrobials to cases that may not benefit. For example, recent studies have shown that approximately 18 to 46% of milk samples obtained from cows that present with clinical mastitis result in culture-negative outcomes (Olde Riekerink et al., 2008; Lago et al., 2011a; Pinzón-Sánchez and Ruegg, 2011), and it is difficult to justify the use of antimicrobial for most of these cases. Mastitis is detected based on observation of inflammation, thus detection may occur after the successful clearance of pathogens by the immune system of the cow and these cases may be not benefit from IMM antimicrobial therapy (Smith et al., 1985; Roberson, 2003). However, microbiologically negative cases may also occur when the animal remains infected but the quantity of colonies that are shed is less than the detection limit of the microbiological method used in the laboratory. In some of these instances, antimicrobial therapy may be beneficial.

Most mastitis presents with mild or moderate symptoms (Oliveira et al., 2013) and few cases are examined or treated by veterinarians (Richert et al., 2013); thus, on most US dairy farms, treatment of mastitis is largely unsupervised by veterinarians. Whereas no compelling evidence exists that the use of IMM antimicrobials results in increased prevalence of resistant pathogens on US dairy farms (Erskine et al., 2002b; Rajala-Schultz et al., 2004; Pol and Ruegg, 2007a), appropriate use of antimicrobials is a public health priority and ensuring judicious usage of antimicrobials in animal agriculture is a societal obligation that must be met.

In spite of concern about usage of antimicrobials in agriculture, few recent studies have described antimicrobial usage in US dairy herds (Zwald et al., 2004; Sawant et al., 2005; Pol and Ruegg, 2007b). Most studies that described treatment practices for clinical mastitis enrolled cases from small herds, were conducted before approval of IMM ceftiofur, or described treatment practices only at herd level. A recent study reported large variations in the use of antimicrobials for treatment of mastitis in 81 Canadian dairy herds (Saini et al., 2012). Similar research has not been recently reported for large dairy herds that are responsible for producing most of the milk in the United States. The objective of the current study was to describe practices used for treatment of clinical mastitis occurring in cows on larger Wisconsin dairy herds.

MATERIALS AND METHODS

Herd and Cow Enrollment Criteria

Recruitment of herds and enrollment of cows has been previously described (Oliveira, 2012; Oliveira et al., 2013). In brief, dairy herds (n = 51) were required to have a minimum of 200 lactating and dry cows, participate in monthly DHI testing, record animal health data into computerized records, use a milking routine that included routine fore-stripping of quarters for detection of mastitis, and administer antimicrobials to treat affected cows without relying on the use of on-farm culture systems. One herd (excluded from analysis in Oliveira et al., 2013) that used an automatic milking system (and therefore did not forestrip all quarters) was allowed to enroll in the study. Data was collected between March and November 2010. Extension agents (n = 18) and practicing veterinarians (n = 2) were trained to collect data about treatment practices and were supervised by university personnel during at least 1 farm visit. During the visit, a questionnaire about treatment practices was administered, and milking technicians on the farms were trained to classify clinical mastitis cases using a standardized severity scoring system (Pinzón-Sánchez and Ruegg, 2011) and were instructed in collection of aseptic quarter milk samples. Cases were classified using the following scale: mild (grade 1), defined as the appearance of abnormal milk only; moderate (grade 2), defined as abnormal milk accompanied by swelling or redness of mammary gland; or severe (grade 3), defined as occurrence of abnormal milk accompanied by systemic signs such depression, anorexia, dehydration, large reduction in milk yield, or fever. After training, farmers were asked to record standardized data for the next 17 cows that experienced clinical mastitis. Each cow could be enrolled in the study once.

Sampling and Data Collection

Collection of data has been previously described (Oliveira, 2012; Oliveira et al., 2013). Most farms identified clinical mastitis by observation of abnormal milk or other symptoms, such as occurrence of a swollen quarter or systemic illness. Trained milking technicians were responsible for case detection and collection of consecutive duplicate quarter milk samples from clinically affected quarter(s) before administration of treatment (**PRE**). After collection of the PRE milk sample,

cows were treated according to individual farm protocol without influence by study personnel. Farm personnel collected a second set of duplicate quarter milk samples from the enrolled quarter(s) at approximately 14 to 21 d after the end of treatment (**POST**). All milk samples were frozen and mailed to University of Wisconsin-Madison's Milk Quality Laboratory. For each case, the following information was collected: date, cow characteristics (parity, calving date), affected quarter(s), severity grade, drugs and doses used for treatment, number of days treated with each drug, date when milk returned to normal appearance ("clinical cure"), date when milk was returned to the bulk tank, occurrence of other diseases, and outcomes of the cases in a 90-d follow-up period.

Microbiological Analysis and Definition of Infection

Microbiological analysis of milk samples has been previously described (Oliveira, 2012; Oliveira et al., 2013) and followed National Mastitis Council guidelines (NMC, 1999). An IMI was defined as the presence of 3 or more identical colonies recovered from a quarter milk sample. Mixed infection was defined as the recovered of at least 3 colonies of 2 different types of bacteria from a sample. Milk samples were considered contaminated if 3 or more dissimilar colony types were found in the same sample. The etiology of cases was defined based on results from duplicate milk samples as described by Pinzón-Sánchez and Ruegg (2011) and Oliveira et al. (2013). Etiologies were defined as (1) results were identical from both duplicate milk samples (92.1% of cases; n = 730); (2) no bacteria were recovered from 1 sample but pathogen was recovered from the other sample (etiology was assigned based on the recovered pathogen; 2.3% of cases; n = 18); (3) 1 sample was contaminated and pathogen was recovered from the other sample (etiology was assigned based on the recovered pathogen; 1.5% of cases; n = 12); (4) 1 sample was contaminated and no bacteria was recovered from the other sample (no growth was assigned; 1.5% of cases; n = 12); or (5) 1 sample was missing but pathogen or no bacteria was recovered from the duplicate (etiology was assigned based on the single sample; 2.6% of cases; n = 21).

Definitions

As previously described (Oliveira et al., 2013), bacteriological cure was assessed by comparing microbiological results of PRE and POST quarter milk samples. Treatment cure was defined when a pathogen was identified on PRE milk sample but POST milk sample was culture negative. Self-cure was defined when no pathogens were recovered from both PRE and POST milk samples (Pinzón-Sánchez and Ruegg, 2011; Oliveira et al., 2013). When a different pathogen was recovered from a POST milk sample, the case was considered a new infection. Enrolled quarters classified as treatment cure and self-cure were categorized together as bacteriological cure. Days until clinical cure was defined as the number of days until the milk returned to normal appearance. Days of milk discard was defined as the number of days the milk was not eligible for sale, including days that milk appeared visibly abnormal, days of treatment, and withholding period of the drug.

Only data from the primary IMM treatment were included in assessment of extra-label drug usage; no systemic antimicrobials have a label indication for mastitis, and thus all systemic treatments were considered to be extra-label. In accordance with US regulations, extra-label antimicrobial use was defined when the duration of treatment was longer than the label specification, when the antimicrobial was used to treat a case caused by a pathogen, which is not included in the label specifications, or when the frequency of treatment differed from the label indication.

Statistical Procedures

Statistical analyses were carried out using SAS version 9.3 (SAS Institute, 2011). Descriptive statistics were used to screen data for errors and observe frequency distributions. The PROC FREQ was used to perform chi-square analyses to determine if each explanatory variable with a categorical distribution was independent of severity scores. In each test, severity score (mild, moderate, or severe) formed the columns of the table and categories of explanatory variables formed the rows of the table. The PROC GLM was used to perform ANOVA tests to determine if each continuous distribution was independent of severity score. The PROC ANOVA was used to determine if the number of days until milk appeared normal was independent of etiology. The PROC LOGISTIC was used to determine if odds of bacteriological cure (yes, no) were associated with selected etiologies (*Escherichia coli*, environmental streptococci, *Klebsiella* spp., *Staphylococcus aureus*, CNS, no growth).

RESULTS

Herd and Case Characteristics

Herd characteristics have been previously described (Oliveira, 2012; Oliveira et al., 2013). In brief, enrolled herds milked 170 to 2,728 cows with an average daily milk yield of 33.5 kg per cow and bulk tank SCC of

219,000 cells/mL. All lactating cows were housed in freestalls and milking was performed in parallel parlors (n = 49), a rotary parlor (n = 1), or with an automatic milking system (**AMS**; n = 1). The farmer that used the AMS was allowed to enroll cows because he manually fore-stripped cows that were suspected of having mastitis. Only 6 cows were enrolled from this herd, and the etiology and severity scores of these cases was similar to cases enrolled from other herds. Other than the herd using the AMS, the milking routine on all farms included removal of foremilk, pre- and postmilking teat disinfection, and drying of teats. All herds used antimicrobial dry cow therapy and most herds also used an internal teat sealant. Written protocols for treatment of mastitis were present on 38 herds and treatments of mastitis were performed by 3.4 people per herd. Use of core-antigen coliform vaccination (2 to 4 times during the lactation) was reported by 22 herds (43%). The minimum number of cases enrolled in the current study was 6 and the maximum was 29; 27 herds enrolled the suggested 17 cows. The distribution of severity scores was approximately 50, 35, and 15% for mild, moderate, and severe cases, respectively (Oliveira et al., 2013).

Microbiological Characteristics of Cases Included in Analysis

The median days from case detection until microbiological analysis at the University of Wisconsin Milk Quality Laboratory was 27, but about 10% of samples were frozen and submitted >98 d after the case was detected. A tendency for a greater proportion of no growth results for these samples was observed (no growth results were obtained for 26 and 38% of samples submitted ≤98 versus >98 d postdetection, respectively; $P = 0.07$). However, no conclusions about the effect of freezing on the results can be drawn from the current study as the results were highly confounded by farm (6 farms contributed virtually all of the late samples).

Cases were enrolled during the seasons of spring (39%), summer (56%), and fall (6%). Overall microbiological results have been previously described (Oliveira, 2012; Oliveira et al., 2013). Whereas duplicate quarter milk samples were collected, the use of a single sample to define the etiology would have resulted in few changes in etiology, indicating that the use of single quarter milk samples to define etiology of mastitis pathogens can be an acceptable methodology. A total of 842 cows were initially enrolled in the current study, but 49 (5.8%) were excluded because ≥2 quarters were simultaneously affected and 46 (5.4%) were excluded because the PRE milk samples were contaminated, leaving a total of 747 cases. No organism was recovered from 27.2% of PRE milk samples. The distribution of pathogens identified in the PRE samples included gram-negative (35.5%), no growth (27.2%), gram-positive (27.6%), and other (9.7%). The most common pathogens included *E. coli* (22.6%), followed by environmental streptococci (12.7%), *Klebsiella* spp. (6.9%), and CNS (6.0%). *Staphylococcus aureus* were recovered from 2.8% of samples.

Characteristics of Treatments

Overall Characteristics. Of the 747 evaluated cases, treatment data was missing for 35 cows. Of cows with treatment data (n = 712), no treatments were administered to 26 cows, only topical treatments were administered to 4 cows, and the affected quarter was therapeutically dried off for 1 cow. Thirty-six cows received only systemic antimicrobials and a variety of IMM antimicrobial treatments (with or without systemic therapy) were recorded for the remaining 645 cows. The distributed IMM treatments were: amoxicillin (n = 26; 4.3%), hetacillin (n = 21; 3.3%), pirlimycin (n = 33; 5.1%), ceftiofur (n = 462; 71.6%), and cephapirin (n = 101; 15.7%). Of cows that received IMM therapy, 138 (21.4%) were also treated with a systemic antimicrobial. Severity scores were not assigned to 123 cases, leaving 589 cases for analysis of treatments by severity (Table 1). The exclusive use of IMM therapy was associated with severity score and was less common for treatment of severe cases of clinical mastitis ($P < 0.001$).

Treatment of Mild Cases of Clinical Mastitis. Of 284 cows from 40 herds that recorded mild cases of clinical mastitis, 20 (7.0%) did not receive any treatment, 4 (1.4%) cows received only topical treatments, and 1 (0.3%) cow had the affected quarter therapeutically dried off (Table 1). Of the 259 cows with mild mastitis that received antimicrobial treatment, 79.9% (n = 207 from 40 herds) were treated only with an IMM antimicrobial and an additional 2% (n = 5 from 2 herds) received only a systemic antimicrobial; 8.1% (n = 21 from 10 herds) received a single IMM antimicrobial in combination with a systemic antimicrobial; and 10.0% (n = 26 from 11 herds) received an additional secondary treatment (either IMM, systemic, or both) because of perceived lack of response to the initial treatment (Table 1).

The compounds used for cows that were treated solely with systemic antimicrobials included oxytetracycline (n = 3) administered for 2 to 3 d or ampicillin (n = 2) administered for 4 to 5; the mean days until clinical cure for those cows was 3.8 (range from 2 to 6). Five compounds (amoxicillin, hetacillin, pirlimycin, ceftiofur, and cephapirin) were administered to cows that were treated only with an IMM antimicrobial (Table

Table 1. Antimicrobial treatments for clinical mastitis by severity grade for 589 cows on 51 dairy herds in Wisconsin

	Severity			
Item, n (%)	Mild	Moderate	Severe	Overall
Herds experiencing mastitis	40 (78.4)	44 (86.3)	29 (56.9)	51 (100.0)
Cows	284 (48.2)	216 (36.7)	89 (15.1)	589 (100.0)
No treatment	20 (7.0)	2 (0.9)	0	22 (3.7)
Topical treatment	4 (1.4)	0	0	4 (0.7)
Teat dry off	1 (0.3)	0	0	1 (0.2)
Cows treated	259 (91.2)	214 (99.0)	89 (100.0)	562 (95.4)
Only IMM[1]	207 (79.9)	146 (68.2)	18 (20.2)	371 (66.0)
Only systemic[2]	5 (1.9)	1 (0.5)	0	6 (1.1)
IMM + systemic[3]	21 (8.1)	31 (14.4)	39 (43.8)	91 (16.2)
Second treatment[4]	26 (10.0)	35 (16.3)	20 (22.5)	81 (14.4)
Two systemic antimicrobials	0	1 (0.5)	12 (13.5)	13 (2.3)
Supportive[5]	21 (8.1)	43 (20.1)	43 (48.3)	107 (18.2)
Systemic sulfadimethoxine	0	6 (2.8)	16 (18.0)	22 (3.7)
Cows receiving only IMM treatment	207 (79.9)	146 (68.2)	18 (20.2)	371 (66.0)
Amoxicillin	12 (4.7)	6 (2.8)	0 (0.0)	18 (4.8)
Hetacillin	11 (4.3)	3 (1.4)	0 (0.0)	14 (19.7)
Pirlimycin	5 (2.0)	5 (2.4)	0 (0.0)	10 (2.7)
Ceftiofur	148 (58.3)	114 (53.8)	16 (20.8)	278 (74.9)
Cephapirin	31 (12.2)	18 (8.5)	2 (2.6)	51 (13.7)

[1]Cows that received only an intramammary (IMM) antimicrobial.

[2]Cows that received only a systemic antimicrobial.

[3]Cows that received an IMM concurrent with a systemic antimicrobial.

[4]Cows that received an additional secondary treatment (either intramammary, systemic, or both) because of perceived lack of response to the initial treatment.

[5]In addition to antimicrobials, proportion of cows that received supportive treatment, such as calcium, fluids, or anti-inflammatories.

1). The most common compounds used were ceftiofur (used for treatment of 148 cows from 31 herds) and cephapirin (used for treatment of 31 cows from 11 herds; Table 2). The mean duration of treatment for cows that were treated only with IMM ceftiofur was 5.0 d and ranged from 1 to 20 d (Table 2). Of cows treated solely with IMM ceftiofur, treatment duration complied with label specifications (1 IMM treatment every 24 h for 2 to 8 consecutive days) for 95.9% of cases (Table 2). Days until clinical cure for cows that received only IMM ceftiofur was 4.5 (range from 2 to 11 d; Table 2); the mean duration of treatment for cows that were treated only with IMM cephapirin was 4.5 d (range from 2 to 8 d; Table 2). Of cows treated only with IMM cephapirin, treatment duration according to the label specifications was followed for 29% of cows (1 IMM treatment every 12 h for 1 d; Table 2). Days until clinical cure for cows that received only IMM cephapirin was 5.2 (range from 2 to 9 d). No difference was observed in days until clinical cure for cows that were treated only with IMM ceftiofur compared with cows that were treated only with IMM cephapirin ($P = 0.114$).

Of cows with mild cases of clinical mastitis that were treated with a single IMM antimicrobial combined with a systemic antimicrobial (n = 21), 18 were treated with IMM ceftiofur and 1 of 5 systemic antimicrobials (ampicillin, ceftiofur, oxytetracycline, penicillin, or a combination of spectinomycin and lincomycin). Ampicillin was the most commonly systemically administered compound. Of cows that were treated with a secondary treatment (n = 26), 18 received a secondary IMM antimicrobial, 1 received 2 additional IMM antimicrobials, 2 received 2 additional systemic antimicrobials, and 5 received 1 additional IMM and 1 systemic antimicrobial. Of these 26 cows, 14 cows were treated primarily with IMM ceftiofur and then received a different combination of antimicrobials (either IMM, systemic, or both; Table 1). Of cows that experienced mild cases of clinical mastitis, 21 cows (8.1%) received supportive therapies, including fluids, calcium, hypertonic saline, and anti-inflammatory drugs (Table 1).

Treatment of Moderate Cases of Clinical Mastitis. Of 216 cows from 44 herds that experienced moderate cases of clinical mastitis, 2 (0.9%) did not receive any treatment (Table 1). Of the cows that received antimicrobial treatment, 68.2% (n = 146 from 40 herds) were treated only with an IMM antimicrobial and an additional 0.5% (n = 1 from 1 herd) received only a systemic antimicrobial; 14.4% (n = 31 from 10 herds) received a single IMM antimicrobial in combination with a systemic antimicrobial; 16.4% (n = 35 from 13 herds) received an additional secondary treatment

Table 2. Selected characteristics of cows receiving only intramammary treatments using ceftiofur (n = 278) or cephapirin (n = 51) for cases of clinical mastitis occurring in cows on 51 dairy herds in Wisconsin

	Severity		
Treatment	Mild	Moderate	Severe
Ceftiofur			
Herds (n)	31	31	12
Number treated	148	114	16
Days treated (range)	5.0 (1–20)	5.4 (1–20)	4.6 (3–8)
Days until clinical cure (range)	4.5 (2–11)	4.4 (1–13)	4.0 (2–6)
Compliance with label for duration of treatment (%)	95.9	93.9	93.9
Cephapirin			
Herds (n)	11	6	1
Number treated	31	18	2
Days treated (range)	4.5 (1–8)	4.9 (1–7)	6.5 (6–7)
Days until clinical cure (range)	5.2 (2–9)	4.5 (3–6)	—[1]
Compliance with label for duration of treatment (%)	29.0	5.6	100

[1]Both animals were culled before milk returned to normal.

(either IMM, systemic, or both) because of perceived lack of response to the initial treatment; and 0.4% (n = 1 from 1 herd) were treated with 2 systemic antimicrobials (Table 1).

One cow was treated only with systemic ampicillin administered for 5 d. The same 5 IMM compounds that were used for treatment of mild cases were administered to cows experiencing moderate cases. The most common IMM compounds were ceftiofur (used for treatment of 114 cows from 31 herds) and cephapirin (used for treatment of 18 cows from 6 herds; Table 2). The mean duration of treatment for cows that were treated only with IMM ceftiofur was 5.4 d (range from 1 to 20 d; Table 2). Of cows treated only with IMM ceftiofur, treatment duration complied with label specifications for 93.9% of cases (Table 2). Days until clinical cure for cows that received only IMM ceftiofur was 4.4 (range from 1 to 13 d); the mean duration of treatment for cows that were treated only with IMM cephapirin was 4.9 d (range from 2 to 7 d; Table 2). Of cows treated only with IMM cephapirin, treatment duration according to the label specification was followed for 5.6% of cows (Table 2); days until clinical cure for cows that received only IMM cephapirin was 4.5 (range from 3 to 6 d; Table 2). No difference in days until clinical cure was observed for cows that were treated only with IMM ceftiofur compared with cows that were treated only with IMM cephapirin ($P = 0.933$).

Of cows that were treated with a single IMM antimicrobial combined with a systemic antimicrobial (n = 31), 29 were treated with IMM ceftiofur and 1 of 4 systemic antimicrobials (ampicillin, ceftiofur, oxytetracycline, or a combination of spectinomycin and lincomycin). Ampicillin was the most commonly administered systemic compound (n = 21). Of cows that were treated with a secondary treatment (n = 35), 21 received a secondary IMM antimicrobial, 3 received 2 additional IMM antimicrobials, 4 received 2 additional systemic antimicrobials, and 7 received 1 additional IMM and other systemic antimicrobials. Of 36 cows, 17 cows were treated primarily with IMM ceftiofur and later received a different combination of antimicrobials (either IMM, systemic, or both; Table 1). Of cows that experienced moderate clinical mastitis cases, 6 cases from 5 farms received systemic sulfadimethoxine for treatment of mastitis caused by *E. coli* (n = 3); *Enterococcus* spp. (n = 1), *Enterobacter* spp. (n = 1), and yeast (n = 1; Table 1). None of the moderate cases treated using sulfadimethoxine had concurrent pneumonia or foot problems nor were any of the cows culled during the 90-d follow-up period. Of cows that experienced moderate clinical mastitis cases, 43 (20.1%) received supportive therapies including fluids, calcium, hypertonic saline, and anti-inflammatory drugs (Table 1).

Treatment of Severe Cases of Clinical Mastitis. Of 89 cows that experienced severe clinical mastitis cases from 29 herds, 13.5% (n = 12) were treated with 2 concurrent systemic antimicrobials, 20.2% (n = 18 from 12 herds) were treated only with an IMM antimicrobial, 43.8% (n = 39 from 13 herds) received a single IMM antimicrobial in combination with a systemic antimicrobial, and 22.5% (n = 20 from 9 herds) received an additional secondary treatment (either IMM, systemic or both) because of perceived lack of response to the initial treatment (Table 1). Only ceftiofur (16 cows from 12 herds) and cephapirin (2 cows from 1 herd) were administered to cows treated only with IMM antimicrobial treatments (Table 2). The mean duration of treatment for cows that were treated only with IMM ceftiofur was 4.6 d (range from 3 to 8 d; Table 2). Of cows treated only with IMM ceftiofur, treatment duration complied with label specifications for 93.9%

of cows (Table 2); days until clinical cure for cows that received solely IMM ceftiofur was 4.0 (range from 2 to 6 d) (Table 2).

Of cows that were treated with a single IMM antimicrobial concurrent with a systemic antimicrobial (n = 39), 37 were treated with IMM ceftiofur and 1 of 6 systemic antimicrobials (ampicillin, ceftiofur, oxytetracycline, sulfadimethoxine, florfenicol, or a combination of spectinomycin and lincomycin). Ampicillin (n = 11 cows) and oxytetracycline (n = 10 cows) were the most common compounds given to these cows. Of cows that were treated with a secondary treatment (n = 20), 2 cows received 2 additional IMM antimicrobials, 13 cows received 2 additional systemic antimicrobials, and 5 cows received 1 additional IMM and 1 additional systemic antimicrobial. Of cows that experienced severe cases of clinical mastitis, 16 cows from 6 separate farms were treated with systemic sulfadimethoxine for mastitis caused by *E. coli* (n = 5), *Klebsiella* spp. (n = 5), or *Pasteurella* spp. (n = 1), whereas 5 additional cases were culture negative. Three of the cows from 1 farm that had received sulfadimethoxine had a record of concurrent illness with either pneumonia or foot rot, which would comply with FDA treatment guidelines. Of the cows with severe mastitis that received systemic sulfadimethoxine, 10 remained in the herd for the 90-d follow-up period, whereas 3 were sold and an additional 3 died. Of cows that experienced severe cases of clinical mastitis, 43 cows (48.3%) received supportive therapies, including fluids, calcium, hypertonic saline, and anti-inflammatory drugs.

Treatments by Etiology

Of cows with severity scores and known etiologies (n = 589), 27 cows received no antimicrobial treatments and 4 cases were missing outcome data leaving 558 cases for analysis of treatments by etiology (Table 3). Of IMM treatments (n = 507), ceftiofur and cephapirin were the most common antimicrobials used for treatment of the primary etiological agents (Table 3). The majority of IMM treatments were administered to cows with a microbiological diagnosis of no growth (34.9%) or *E. coli* (27.2%). Of cows that were treated with antimicrobials (either IMM or systemic), days until clinical cure was greater for cases caused by *E. coli* (6.4 d) and environmental streptococci (5.3 d) as compared with cases with other microbiological diagnoses (Table 3). For cases caused by gram-positive pathogens, days until clinical cure were 5.3, 3.9, and 3.8 for cases caused by environmental streptococci, CNS, and *Staph. aureus*, respectively, and no difference was noted in days until clinical cure among cases caused by these pathogens (Table 3). Half of the cows experiencing cases caused by *E. coli* were treated using systemic antimicrobials in contrast to only 6.8% of cows with cases caused by CNS (Table 3). Of cows with mastitis caused by *Staph. aureus*, 26.1% were treated with systemic antimicrobials (Table 3). Based on results of the logistic regression model, bacteriological cure was associated with etiology (Table 2; $P < 0.001$). The odds of bacteriological cure were less for cases caused by environmental streptococci and *Staph. aureus* as compared with cases that had no microbiological growth (Table 3).

In almost all instances, treatments were likely administered without knowledge of the causative pathogen. Thus, based on the pathogens specified on product labels, all treatments where no pathogens were recovered or that were caused by *Klebsiella* spp. were categorized as extra-label treatments (Table 3). Of cows experiencing cases caused by *Staph. aureus* and treated with IMM antimicrobial, 81.8% received extra-label treatment (primarily due to treatment with IMM ceftiofur). Of cows experiencing cases caused by *E. coli* and treated with IMM antimicrobial, 27.5% received extra-label treatment (Table 3).

DISCUSSION

The reference population for the current study is larger dairy farms that have primarily controlled traditional contagious pathogens, such as *Staph. aureus* and *Streptococcus agalactiae*. The shift to environmental pathogens associated with clinical mastitis on US dairy herd was first documented over 20 yr ago (Hogan et al., 1989). In the present study, most pathogens were opportunistic environmental organisms, such as *E. coli*, streptococci, *Klebsiella* spp., and CNS. Whereas cases were enrolled only in spring, summer, and fall, the distribution of pathogens observed in our study is similar to other studies that have included milk samples from clinical mastitis cases of cows on larger modern US dairy farms (Lago et al., 2011a; Pinzón-Sánchez and Ruegg, 2011; Schukken et al., 2011). The distribution of pathogens indicates the importance of understanding how to implement effective treatment programs for mastitis caused by a diverse group of environmental organisms.

In the United States, with the exception of some severe cases of mastitis, few veterinarians are actively involved in administration of treatments for bovine mastitis (Richert et al., 2103). Regulations regarding administration of antimicrobials to dairy cows are complex and a review of these regulations is beyond the scope of this paper. Depending on the compound, antimicrobials may be classified as over the counter (for example, commercially prepared IMM cephaparin), prescription (for example, commercially prepared IMM

Table 3. Antimicrobial treatments by etiology determined using milk samples collected at detection for cases of clinical mastitis occurring in cows on 51 dairy herds in Wisconsin

Microbiological diagnosis	Cases diagnosed	Cows treated (n)	Days until clinical cure[1]	Received systemic therapy (%)	Cows treated with intramammary antimicrobial[2] (n)					BC[3] (%)	Odds of BC[4]	CI for odds ratio
					AM	HE	PI	CF	CP			
Escherichia coli	167	161	6.4[a]	50.3	6	3	6	106	17	74.6	1.07	(0.57–2.03)
Klebsiella spp.	52	49	4.4[b]	36.7	0	1	0	39	7	78.2	1.31	(0.45–3.82)
Environmental streptococci	95	85	5.3[ab]	8.2	5	1	7	47	21	51.9	0.39	(0.20–0.77)
CNS	45	44	3.9[b]	6.8	2	3	6	25	6	55.9	0.46	(0.21–1.01)
Staphylococcus aureus	23	23	3.8[b]	26.1	2	1	2	14	3	25.0	0.12	(0.04–0.40)
No growth	203	196	4.3[b]	12.7	6	8	5	129	29	73.3	1.00	Referent

[a,b]Means within a column with the same superscript are not significantly different ($P < 0.05$).

[1]Analysis performed on 71, 21, 39, 32, 16, and 108 cases of *E. coli*, *Klebsiella* spp., environmental streptococci, CNS, *Staph. aureus*, and no growth cases, respectively.

[2]AM = amoxicillin (label indications for treatment of *Streptococcus agalactiae* and *Staph. aureus*); HE = hetacillin (label indications for treatment of *Strep. agalactiae*, *Staph. aureus*, *Strep. dysgalactiae*, and *E. coli*); PI = pirlimycin (label indications for treatment of *Staphylococcus* and *Streptococcus* spp.); CF = ceftiofur (label indications for treatment of *E. coli*, CNS, and *Streptococcus dysgalactiae*); CP = cephapirin (label indications for treatment of *Staph. aureus* and *Strep. agalactiae*).

[3]BC = bacteriological cure. Analysis performed on 83, 23, 52, 34, 16, and 120 cases of *E. coli*, *Klebsiella* spp., environmental streptococci, CNS, *Staph. aureus,* and no growth cases, respectively.

[4]Reference level is BC for no growth cases.

ceftiofur), allowable under extra-label usage guidelines defined by the herd veterinarian (for example, systemic usage of ampicillin for treatment of severe mastitis), or not allowed under any circumstances (for example, administration of sulfonamides for treatment of mastitis). All of these classifications of usage were noted in our study. It is important to note that extra-label drug usage is an acceptable practice in the United States, but it is vital that veterinarians are actively involved in prescribing and supervising drugs that are used in this manner. Continued education of farmers and veterinarians is necessary to ensure that extra-label drug usage is necessary for a particular case and will contribute to improved dairy animal welfare.

In the current study, many of the cows that experienced microbiologically negative cases of clinical mastitis received IMM antimicrobial treatment and 12.7% received systemic treatment. Many opportunistic organisms that cause mastitis are successfully eliminated by the immune response of the cow, and the shift in etiologies indicates that a large opportunity to reduce the use of antimicrobials for treatment of clinical mastitis exists. It is difficult to justify the use of antimicrobials to treat most cases of mastitis that are culture negative when detected, and the cow likely experiences little benefit. The usefulness of administration of IMM antimicrobials to treat animals experiencing mild and moderate cases of mastitis caused by *E. coli* is also questionable because of the high rate of spontaneous cure (Roberson et al., 2004; Wagner and Erskine, 2009; Suojala et al., 2013). Some researchers have reported no difference in bacteriological cure rates for untreated cows compared with cows treated for mastitis caused by gram-negative pathogens, and the majority of antimicrobials labeled to treat mastitis have limited activity against these organisms (Pyörälä, 1988; Pyörälä et al., 1994; Suojala et al., 2013). A multiherd clinical trial compared outcomes of a treatment protocol based on on-farm culture (cases caused by gram-negative pathogens or no pathogen recovered were not treated) to outcomes of cows in a positive control group where all cases were treated with cephapirin (regardless of etiology; Lago et al., 2011a,b). The use of an on-farm culture system to guide the strategic treatment of nonsevere clinical mastitis reduced IMM antimicrobial use by about half without significant differences in days to clinical cure, bacteriological cure risk, new IMM infection risk, or treatment failure risk within 21 d after the clinical mastitis event (Lago et al., 2011a). Researchers have reported greater bacteriological cure for clinical mastitis caused by a variety of gram-negative pathogens treated using IMM ceftiofur (compared with nontreated control cows); however, treatment did not significantly influence SCC or milk yield in the remainder of the lactation (Schukken et al., 2011). Increased use of rapid diagnostic methods (such as culture on the farm or in local veterinary clinics) to guide treatment decisions for nonsevere cases of clinical mastitis has the potential to improve judicious usage of IMM therapies and reduce antimicrobial usage on dairy farms.

Specific treatment protocols were not used as a criterion to enroll herds in the current study because the objective was to characterize treatments currently used on commercial dairy herds. Thus, treatment protocols

varied greatly among herds. Whereas it is possible that some farmers may not have recorded all treatments that were administered to a cow, the case forms were checked against computerized records and generally agree with treatments that have been recorded in previous studies conducted on similar farms in this region. Variation in the use of antimicrobials to treat clinical mastitis among dairy herds was also observed by Pol and Ruegg (2007b), González et al. (2010), and Saini et al. (2012). In the current study, 5 different IMM drugs were used among herds, but the majority of treatments were performed with ceftiofur or cephapirin. Ceftiofur is a broad-spectrum, third-generation cephalosporin. Several systemic products containing ceftiofur are available in the United States and do not have withdrawal periods for milk, thus they are extensively used (Erskine et al., 2002a). The IMM formulation of ceftiofur is labeled for treatment of clinical mastitis caused by CNS, *Streptococcus dysgalactiae*, and *E. coli* and has a milk withdrawal period of 72 h. Whereas ceftiofur has the broadest spectrum of any currently available IMM compound used in the United States, it would not be expected to be effective for many of the diverse environmental pathogens that caused mastitis in the present study. Regardless of route of administration, FDA regulations allow only limited extra-label usage of ceftiofur.

Before approval of IMM ceftiofur in 2006, cephapirin was the most common IMM drug used to treat clinical mastitis (Sawant et al., 2005; Raymond et al., 2006; Pol and Ruegg, 2007b). Cephapirin is available only as an IMM preparation and has a longer withdrawal period (96 h) and a short recommended duration of treatment (2 doses, 12-h interval) as compared with IMM ceftiofur. Cephapirin is labeled for treatment of clinical mastitis caused by *Staph. aureus* and *Strep. agalactiae*; however, as a first-generation cephalosporin, cephapirin should be effective for most gram-positive mastitis pathogens (Cortinhas et al., 2013). In the present study, *Staph. aureus* was responsible for only 3.1% cases of clinical mastitis and no *Strep. agalactiae* were isolated from enrolled cows. Only a minority of treatments using IMM cephapirin were performed following label directions for duration. Overall, when the FDA guidelines for extra-label usage are strictly interpreted, the proportion of extra-label treatments ranged from 30 to 100% of cases of clinical mastitis (based on label specifications for pathogens, frequency of treatment, or duration of treatment). Currently, no IMM antimicrobials are labeled for treatment of cases caused by *Klebsiella* spp., thus 100% of cases caused by *Klebsiella* spp. could be considered extra-label treatments. Among cows that received primary IMM treatment, approximately 16% of cows received a single IMM antimicrobial concomitant with a systemic antimicrobial. All systemically administered antimicrobials used for treatment of mastitis are considered extra-label treatments and thus must be used under the direction of a veterinarian. It is not likely that most of the products that were given systemically were able to achieve and sustain a therapeutic concentration in the mammary gland. For example, at normal doses, systemically administered sulfonamides, penicillin, aminoglycosides, and cephalosporins do not readily distribute into the mammary gland (Erskine et al., 2003). However, for cows experiencing severe symptoms of clinical mastitis, use of a systemic antimicrobial could improve the clinical outcomes by reducing the occurrence of bacteremia (Wenz et al., 2001; Erskine et al., 2002a). Erskine et al. (2002a) investigated the use of ceftiofur administered systemically in 104 cows with severe clinical mastitis. They concluded that systemic use of ceftiofur for treatment of mastitis caused by coliforms reduced the proportion of cow deaths and culling but did not affect the outcome for cases caused by other pathogens.

Of cows enrolled in the current study, 13.4% received a secondary antimicrobial treatment because of perceived lack of response to the initial treatment. Severe cases received the majority of secondary treatments. Farmers may switch mastitis treatments because they perceive that a treatment is not effective. However, it is difficult for farm personnel to perceive efficacy of mastitis treatments. Inflammation is often self-limiting after 4 to 6 d and is not always predictive of the presence of active IMI or the need for additional therapies. Outcomes after the use of multiple therapies used for treatment of mastitis have not been well described, thus recommendations for when to change or extend therapy are based primarily on clinical experiences; research to better define appropriate outcomes and indicators of when addition therapy is warranted.

Sulfadimethoxine is labeled only for treatment of pneumonia or foot infections and no extra-label usage of this compound is permitted. Similar to other studies (Sawant et al., 2005; Pol and Ruegg, 2007b), sulfadimethoxine was used to treat 22 cows experiencing mastitis on 8 separate dairy farms. Of cows that received this compound, only 3 cows experienced mastitis concurrent with pneumonia or foot rot; thus, treatments of the other cows were in violation of FDA policy, indicating the continued need for education of both veterinarians and dairy producers about proper drug usage on dairy farms.

CONCLUSIONS

Almost all cases of clinical mastitis were treated using IMM antimicrobials without knowledge of etiology.

Whereas 5 different compounds were used for IMM treatment, the majority of treatments used a third-generation cephalosporin. Treatments were administered for 4 to 6 d and, regardless of etiology, milk remained abnormal for about the same period. The most common use of IMM antimicrobial was for treatment of a microbiologically negative case. Many of the antimicrobials used for systemic treatment would not be expected to achieve a therapeutic concentration in the mammary gland. Many treatments would be considered as extra-label treatments and, in spite of FDA prohibitions, 8 farms used sulfonamides for treatment of mastitis. A large opportunity exists for improvements in the use of antimicrobials for treatment of bovine mastitis.

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