Analysis of puerperal metritis treatment records in a grazing dairy farm in Argentina

Analyse der Aufzeichnungen zur Behandlung puerperaler Metritiden von Kühen in einem Milchviehbetrieb mit Weidehaltung in Argentinien

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ZUSAMMENFASSUNG

Ziel Bewertung der Wirksamkeit von Antibiotika zur Behandlung der puerperalen Metritis (PM) und ihres Effekt auf die Reproduktionsleistung von Milchkühen.

Material und Methoden Die retrospektive Kohortenstudie wertete 9168 Datensätzen von Kühen eines Milchviehbetriebs mit ganzjähriger Weidehaltung in Argentinien aus. Es handelte sich um Kühe mit einer PM 3. Grades (PM3, diagnostiziert mittels Metricheck, Skala 0–3), die 0–21 Tage post partum (p. p.) mit Ceftiofur (freie kristalline Säure, 6,6 mg/kg) behandelt worden waren (n = 2688), sowie unbehandelte Kühe mit einer PM 1. und 2. Grades (PM1–2; n = 6480). Alle Kühe wurden 21 Tage p. p. erneut mittels Metricheck untersucht, um die klinische Heilung (Vaginalausfluss [VD], Score 0), eine teilweise Heilung (VD-Score gleich oder niedriger als zuvor) oder keine Heilung (VD-Score höher als zuvor) festzustellen. Bei Kühen mit VD1–3 wurde die Diagnose klinische Endometritis (KE) 1–3 gestellt. Das Auftreten von PM1–3, die Heilungsrate, die Güstzeit, das Risiko einer Trächtigkeit, einer nicht eintretenden Trächtigkeit sowie einer KE wurden mittels SAS-Software analysiert.

Ergebnisse Die finale Auswertung berücksichtigte 8876 Datensätze (PM3: n = 2435, 27,43 %; PM1–2: n = 6441, 72,57 %). Kühe mit PM1 und PM2 wurden 14 bzw. 12 Tage früher trächtig als Kühe mit PM3 ($p < 0,001$). Die mit Ceftiofur behandelten PM3-Kühe wiesen zu 24,85 % eine klinische Heilung auf, zu 53,63 % eine teilweise Heilung und zu 18,52 % keine Heilung. Dagegen ergab sich bei Kühen mit PM1–2 eine Heilungsrate von 51,96 %, eine teilweise Heilung bei 20,70 % und keine Heilung bei 24,53 % ($p < 0,001$). Vollständig geheilte Kühe wurden 13 bzw. 11 Tage früher trächtig als teilweise oder nicht geheilte Kühe ($p < 0,001$). Bei Kühen mit PM3 in den ersten 21 Tagen p. p. war im Vergleich zu Kühen mit PM 1–2 die Wahrscheinlichkeit, später eine KE zu entwickeln, doppelt so groß (41,28 % vs. 24,14 %, $p < 0,001$). Weniger als 1 % der Kühe mit klinischer Heilung wiesen später eine KE auf. Bei Tieren mit teilweiser oder ohne Heilung betrug dieser Anteil 63,32 % bzw. 38,21 % ($p < 0,001$).

Schlussfolgerung und klinische Relevanz Nach der Ceftiofur-Behandlung galten 78 % der PM3-Kühe als geheilt, wenn die Heilung als fehlender übelriechender VD beurteilt wurde. Als vollständig geheilt (klarer Ausfluss) wurden jedoch nur 25 % der Kühe bewertet. Kühe mit diagnostizierter Metritis bei der Nachuntersuchung hatten nach mehr als 21 Tagen p. p. ein höheres Risiko einer KE und längere Güstzeiten als Kühe mit physiologischem klarem VD.

ABSTRACT

Objective To assess the efficacy of antibiotic usage for the treatment of puerperal metritis (PM) and its association with reproductive performance, a retrospective cohort study including a total of 9168 records of cows from a dairy farm in Argentina was run.

Material and methods Cows having a PM3 (metricheck, scale 0–3) and treated with ceftiofur (ceftiofur crystalline free acid, 6.6 mg/kg) at 0–21 days postpartum (p. p.) (n = 2688), and cows having a PM 1–2 and not treated with an antibiotic at 0–21 days p. p. (n = 6480) were included in the study. All cows were reexamined with metricheck to assess the clinical cure (vaginal discharge [VD] score 0), partial cure (VD score similar or lower than previous), no cure (VD score higher than previous). Cows with a metricheck VD1–3 after 0–21 days p. p. were diagnosed as clinical endometritis (CE) 1–3. The occurrence of PM1–3, cure rate, calving to conception interval, the hazard of pregnancy, odds for non-pregnancy, and odds for CE were analyzed using SAS software.

Results A total of 8876 PM1–3 records were included, 2435 records of PM3 treatments with ceftiofur (27.43 %), and 6441 records of PM1–2 (72.57 %) with no treatment. Cows having PM1 and PM2 became pregnant 14 and 12 days earlier than cows with PM3 ($p < 0.001$). The PM3 ceftiofur treated cows had a clinical cure of 24.85 % (PM0); 53.63 % had a partially cure; and 18.52 % no cure. Conversely, cows with PM1–2 had a 51.96 %, 20.70 %, and 24.53 % cure rate, respectively ($p < 0.001$). Cows having complete cure became pregnant 13 and 11 days earlier than cows having partial cure and no cure ($p < 0.001$). Cows that had PM3 during the first 21 days p. p. had twice the chances of developing CE compared to cows having PM1–2 (41.28 % vs. 24.14 %, $p < 0.001$). After 21 days p. p., less than 1 % of cows with clinical cure developed CE compared to 63.32 % that developed CE with partial cure, and 38.21 % with no cure ($p < 0.001$).

Conclusion and clinical relevance After ceftiofur treatment, 78 % of cows were cured when measured by disappearance of fetid VD but only 25 % of cows had clinical cure when measured by appearance of a clear VD. The cows that remained with clinical metritis had more chances of having CE after 21 days p. p. and had more days open than cows with clear normal VD.

Introduction

Puerperal metritis (PM) is one of the most common and the costliest postpartum diseases in dairy cows [1][2][3]. It reduces fertility and milk production [2][4], and rises treatment cost, discarded milk costs, and labor costs [2][4]. Furthermore, PM increases the number of dead or culled cows from the herd during the first 100 days of lactation which is the most profitable period of a dairy cow lactation and therefore increasing replacement costs [2][5][6].

The definition and diagnosis of PM was revised almost a decade ago [7]. Cows during the 1st week postpartum (p. p.) should be examined with a speculum, a metricheck, or hand gloved for type and smell of vaginal discharge (VD) [1][3][7][8][9]. A cow with reduced milk production, dullness, watery brownish fetid VD and with a rectal temperature > 39.5 °C is defined as having PM and requires prompt treatment with antibiotics (ATB) and supportive therapy when necessary [1][3][7][8]. Conversely, a cow without hyperthermia, but with an enlarged uterus and abnormal VD, is characterized as having clinical metritis (CM) [3][7]. Calving related disorders such as abortion or stillbirth, dystocia, twins, retained fetal membranes, acute hypocalcemia, rise in negative energy balance and ketosis have been described as major risk factors for developing PM during the first 10 days p. p. [3][10].

Treatment strategies for PM have been a topic of great controversy during the last decade. Systemic ATB alone or in combination with non-steroidal anti-inflammatory drugs (NSAID) are the treatments of choice for PM [7]. The most used ATB for systemic therapy of PM are third-generation cephalosporins, penicillin procaine, ampicillin, oxytetracycline, or a combination of ampicillin with oxytetracycline or cloxacillin [11][12]. Also, intrauterine infusions with penicillin procaine or oxytetracycline are used in some dairy practices [12]. However, the majority of clinical trials during the last 2 decades have reported the use of 2 primary ATB for treatment of PM in dairy cows which are ceftiofur (ceftiofur hydrochloride, 2.2 mg/kg; ceftiofur sodium, 2.2 mg/kg; ceftiofur crystalline free acid, 6.6 mg/kg) [1][3][8][9][12][14] and ampicillin (11 mg/kg) [12][15]. Most authors agree that only cows with reduced milk production, dullness, watery brownish fetid VD, and a rectal temperature higher than 39.5 °C should be treated with an ATB (PM) [1][3][8]. However, a recent large study in 45 California dairies showed that 70 % of dairies performed rectal exams for VD evaluation; and that only 25 % based systemic ATB administration on the presence of fever regardless of odor or abnormal VD, 2 % on the presence of fetid VD and pyrexia (2 %), and 9 % on the presence of fetid VD or pyrexia [12].

Prudent use of ATB in dairy production medicine in general and in the treatment of PM, in particular, is becoming an important issue to minimize the risk of antimicrobial-resistant organisms and to minimize the risk of antimicrobial residues in dairy products [12][16]. Dairy practitioners must use the proper combination of diagnostic methods and ATB selection to maximize the cure rate and minimize antimicrobial resistance (AMR) and antimicrobial residues in milk. Sometimes this information is scarce and not readily available to the practitioner. Most recently, a meta-analysis has been used to systematically analyze and summarize an extensive collection of randomized clinical trials on ATB treatment of metritis in dairy cows [16]. The most important finding was that the ceftiofur treatment of metritic cows was associated with a decrease in the prevalence of metritis following therapy in comparison to untreated cows. However, this study also concluded that the comparison of different ATB treatments and the efficacy of ATB versus non-ATB drugs concerning metritis prevalence at the time of reexamination was not analyzed because of the lack of comparable trials [16].

In recent years, the digitalization, collection, and storage of vast quantities of data, in combination with advances in data science

▸ **Table 1** Occurrence of puerperal metritis (PM) score 1–3 diagnosed by metricheck at 0–21 days postpartum by parity.

▸ **Tab. 1** Auftreten der puerperalen Metritis Score 1–3 diagnostiziert mittels Metricheck 0–21 Tage post partum in der 1. bis ≥ 3. Laktation.

PM score	Lactation 1	Lactation 2	Lactation 3 +	Total
3	33.48 % (1419/4238)	20.10 % (428/2129)	23.44 % (588/2509)	27.43 % (2435/8876)
2	43.61 % (1848/44 238)	48.94 % (1042/2129)	44.68 % (1121/2509)	45.19 % (4011/8876)
1	22.91 % (971/4238)	30.95 % (659/2129)	31.89 % (800/2509)	27.38 % (2430/8876)
Total	47.75 % (4238/8876)	23.99 % (2129/8876)	28.27 % (2509/8876)	100.00 % (8876)

Lactation effect, $p < 0.001$

has opened a new era of big data. In One Medicine-One Health, routine collection of large amounts of clinical data/big data is becoming more common, as are research studies that make use of these data sources [17][18]. The use of big data provides the opportunity to address clinical questions, identify risk factors, and do retrospective studies to strengthen evidence-based medicine [19]. Also, digitalization accelerates sharing of anonymous data and allows participating farmers and practitioners to compare and benchmark against other participants in the same area in term of demographics, diseases, treatments, productive and reproductive results [19]. Most of the modern dairy farms have a record-keeping system where cow information is stored during lactation, allowing to retrieve data and make management or treatment decision based upon production, reproduction and health events stored (e. g., Dairy Comp® Vas, Alta Waterfront, WI, USA; Pro Tambo Master®, DIRSA, Gonnet, Argentina). We recently studied the relationship between individual cow milk yield and fertility, accounting for the contextual effect of the herd using a data set that included 657 968 lactations from 677 dairy herds in Argentina from 2001 to 2012 [20]. A similar study could be done using the PM treatment records to analyze clinical cure rate, partial cure rate, and no cure rate; and to benchmark the productive and reproductive efficiency of treated and untreated animals.

Hence, in summary, big data of treatment records of PM in dairy farms have been available for many years. Still, there has not been any retrospective study to analyze these records to respond to clinical questions about cure rate, risk factors, and benchmark demographics, treatments, and productive and reproductive efficiency of treated and untreated animals. Therefore, the objective of this study was to assess the efficacy of ATB usage for the treatment of PM and its association with reproductive performance in a herd of grazing dairy cows.

Material and methods

Data collection A retrospective cohort study, including a total of 9168 records of cows calving from January 1st, 2010 to December 31st, 2016, from a dairy farm in Argentina (~2800 milking cows) was run. All cows were diagnosed with a metricheck for PM within the 1st week of lactation using a 1–3 scale [3]. Included records were those having an episode of PM score 3 diagnosed by metricheck and treated with an ATB at 0–21 days p. p. (n = 2688), and those having an episode of PM score 1–2 diagnosed by metricheck and not treated with an ATB at 0–21 days p. p. (n = 6480).

Treatment and results All cows diagnosed with PM score 3 received a ceftiofur treatment according to manufacturer recommendation (ceftiofur crystalline free acid, 6.6 mg/kg; Excede®, Zoetis, Argentina). All diagnosed cows were reexamined with metricheck at weekly intervals to confirm case remission. Cows that were not available to metricheck diagnosis the next veterinary visit were classified as missed check. Cows with a metricheck PM score 0 were diagnosed as clinical cure, cows with a metricheck PM score similar or lower than previous were diagnosed as partial cure, cows with a metricheck PM score higher than previous were diagnosed no cure, and cows with VD 1–3 21 days p. p. were diagnosed as clinical endometritis (CE) 1–3 [21]. All cows diagnosed with CE were treated once with cephapirin benzathine (500 mg; Metricure®, MSD, Argentina).

Statistical analysis Data were analyzed with the SAS software package [22]. The occurrence of PM score 1–3 and the cure rate were estimated with Proc Freq of SAS. The calving to conception interval was estimated with Proc Lifetest of SAS. The hazard of pregnancy was estimated with Proc PHReg of SAS. Finally, the odds for non-pregnancy and the odd for CE was estimated with Proc Glimmix of SAS with binomial distribution and logit link function. Assessed risk factors were parity (1 vs. 2 vs. ≥ 3), the season of PM (summer vs. fall vs. winter vs. spring), and clinical cure rate (clinical cure vs. partial cure and no cure). Statistical significance was set at $p < 0.05$.

Results

After editing all records, 292 records of PM score 1–3 were removed from the analysis because of incomplete records. The final statistical analysis included a total of 8876 PM score 1–3 records, corresponding 6441 records to PM score 1–2 (72.57 %) that received no ATB treatment, and 2435 records to PM score 3 that were treated with ceftiofur (27.43 %).

▸ **Table 2** Occurrence of puerperal metritis (PM) score 1–3 diagnosed by metricheck at 0–21 days postpartum by season.

▸ **Tab. 2** Auftreten der puerperalen Metritis (PM) Score 1–3, diagnostiziert mittels Metricheck 0–21 Tage nach der Geburt, dargestellt für die jeweilige Jahreszeit.

PM score	Summer	Fall	Winter	Spring	Total
3	27.80 % (637/2291)	25.12 % (597/2377)	27.41 % (606/2211)	29.79 % (595/1997)	27.43 % (2435/8876)
2	46.18 % (1058/2291)	45.27 % (1076/2377)	45.32 % (1002/2211)	43.82 % (875/1997)	45.19 % (4011/8876)
1	26.01 % (596/2291)	29.62 % (704/2377)	27.27 % (603/2211)	26.39 % (527/1997)	27.38 % (2430/8876)
Total	25.81 % (2291/8876)	26.78 % (2377/8876)	24.91 % (2211/8876)	22.50 % (1997/8876)	100.00 % (8876)

Season effect, p < 0.001

Occurrence of puerperal metritis

First lactation cows had a 2-day shorter interval from calving to the PM case compared to 2nd and 3 rd plus lactations (8.37 ± 0.05 vs. 10.43 ± 0.07 days, p < 0.0001). Similarly, although it was not biologically meaningful, there was a statistically significant difference between seasons (range, 9.37 ± 0.07 to 9.89 ± 0.09 days, p < 0.001).

First lactation cows had an 11.58 % higher occurrence of PM score 3 compared to 2nd and 3 rd plus lactation cows (33.48 % vs. 21.90 %, p < 0.001, ▸ **Table 1**). Furthermore, cows calving in spring had a 3.05 % higher occurrence of PM score 3 compared to cows calving in summer, fall, and winter (29.79 % vs. 26.74 %, p < 0.001; ▸ **Table 2**).

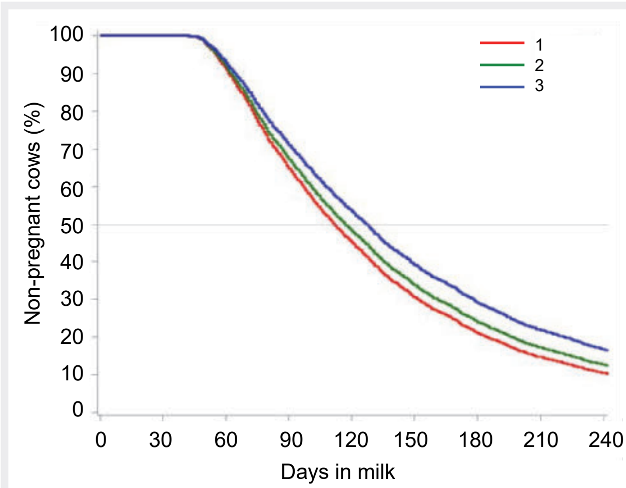
Pregnancy

Cows having PM score 1 and PM score 2 became pregnant 14 days and 12 days earlier than cows with PM score 3 (median, 95 % CI; PM1, 111 days, 106–114; PM2, 113 days, 111–117; and PM3, 125 days, 120–129; p < 0.001; ▸ **Fig. 1**). Furthermore, cows with PM score 2 or PM score 3 had lower hazard of pregnancy than herd mates with PM score 1 (hazard ratio [HR] = 0.91, 95 % CI = 0.86–0.97; HR = 0.78, 95 % CI = 0.73–0.84; respectively; p < 0.001).

Cure rate

Approximately 3 % of the cows were not available for the metricheck diagnosis at the next veterinary visit (73/2435) (▸ **Table 3**). The PM score 3 ceftiofur treated cows had a clinical cure rate of 24.85 % (605/2435); 53.63 % were partially cured (1306/2435); and 18.52 % were not cured (451/2435). On the other hand, cows with PM score 1–2 had a 51.96 % (3343/6441), 20.70 % (1333/6441), and 24.53 % (1580/6441) cure rate, respectively (p < 0.001) (▸ **Table 3**). Cows with a partial cure had 80 % fewer chances of cure compared to cows with clinical cure (0.18 ± 0.16–0.20, p < 0.0001). Likewise, cows with no cure had almost 30 % less chances of cure compared to cows with clinical cure (0.73 ± 0.66–0.82, p < 0.0001) (▸ **Table 4**).

Cows with complete cure (PM score 0) became pregnant 13 days and 11 days earlier than cows partially cured and cows not cured (median, 95 % CI; complete cure, 109 days, 106–112; partial cure, 122 days, 117–126; no cure, 120 days, 116–125; p < 0.001;



▸ **Fig. 1** Calving to pregnancy interval in grazing dairy cows (n = 7195) from a commercial farm in Argentina experiencing puerperal metritis (PM) metricheck score 1 (red line, n = 3381), PM metricheck 2 (green line, n = 2139), or PM metricheck score 3 (blue line, n = 1675). Cows with PM score 1 had shorter calving to pregnancy interval (median, 95 % CI; 111 days, 106–114) than cows PM score 2 (113 days, 111–117), and PM score 3 (125 days, 120–129); p < 0.001]. Cows with PM score 2 or score 3 had lower hazard of pregnancy than herd mates with score 1 (hazard ratio [HR] = 0.91, 95 % CI = 0.86–0.97; HR = 0.78, 95 % CI = 0.73–0.84; respectively; p < 0.001). Source: © R. L. de la Sota.

▸ **Abb. 1** Güstzeit von Milchkühen (n = 7195) in einem kommerziellen Milchviehbetrieb mit Weidehaltung in Argentinien. Puerperale Metritis (PM), diagnostiziert mittels Metricheck, Score 1 (rote Linie, n = 3381), Score 2 (grüne Linie, n = 2139), Score 3 (blaue Linie, n = 1675). Kühe mit PM Score 1 hatten kürzere Güstzeiten (Median 95 % CI; 111 Tage, 106–114) als Kühe mit Metritis-Score 2 (113 Tage, 111–117) und Metritis-Score 3 (125 Tage, 120–129); p < 0,001]. Kühe mit Metritis-Score 2 oder Score 3 hatten eine geringere Wahrscheinlichkeit einer Trächtigkeit als Tiere mit Score 1 (Hazard Ratio [HR] = 0,91, 95 %-KI = 0,86–0,97; HR = 0,78, 95 %-KI = 0,73–0,84; p < 0,001). Quelle: © R. L. de la Sota.

▶ **Table 3** Observed cure rate of puerperal metritis (PM) score 1–3 diagnosed by metricheck at 0–21 days postpartum and confirmed cured the next visit.

▶ **Tab. 3** Heilungsraten puerperaler Metritiden (PM) Score 1–3, diagnostiziert mittels Metricheck, 0–21 Tage post partum und bei einer Folgeuntersuchung beurteilt.

PM score	Missed check	Clinical cure	Partial cure	No cure	Total
3	3.00 % (73/2435)	24.85 % (605/2435)	63.63 % (1306/2435)	18.52 % (451/2435)	27.43 % (2435/8876)
2	3.12 % (125/4011)	46.40 % (1861/4011)	27.60 % (1107/4011)	22.89 % (918/4011)	45.19 % (4011/8876)
1	2.47 % (60/2430)	60.99 % (1482/2430)	9.30 % (226/2430)	27.24 % (662/2430)	27.38 % (2430/8876)
Total	2.91 % (258/8876)	44.48 % (3948/8876)	29.73 % (2639/8876)	22.58 % (2031/8876)	100.00 % (8876)

Missed check: cow was not available to metricheck diagnosis the next veterinary visit; clinical cure: cow was diagnosed by metricheck with PM score 0; partial cure: cow was diagnosed by metricheck with PM score similar or lower than previous; no cure: cow was diagnosed by metricheck with PM score higher than previous.

▶ **Table 4** Logistic model assessing risk factors for cure rate of puerperal metritis (PM) score 1–3 diagnosed by metricheck at 0–21 days postpartum in grazing dairy cows (n = 8618).

▶ **Tab. 4** Logistisches Modell zur Bewertung der Risikofaktoren für die Heilungsraten puerperaler Metritiden (PM) Score 1–3, diagnostiziert mittels Metricheck, 0–21 Tage post partum bei Milchkühen in Weidehaltung (n = 8618).

Effect	Level	Odds ratio	95 % CI	P
Lactation	1	1		< 0.0001
	2	1.60	1.43–1.78	
	3	1.57	1.41–1.74	
Season	Summer	1		< 0.0001
	Fall	1.27	1.12–1.43	
	Winter	1.26	1.11–1.43	
	Spring	1.02	0.89–1.16	
Cure	Clinical cure	1		< 0.0001
	Partial cure	0.18	0.16–0.20	
	No cure	0.73	0.66–0.82	

95 %CI: 95 % confidence Interval; P: probability
Clinical cure: cow was diagnosed by metricheck with PM score 0; partial cure: cow was diagnosed by metricheck with PM score similar or lower than previous; no cure: cow was diagnosed by metricheck with PM score higher than previous.

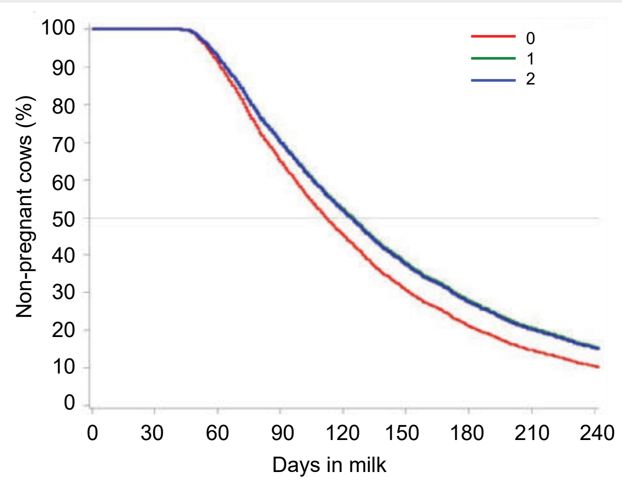
▶ **Fig. 2**). Furthermore, cows with partial cure or no cure had lower hazard of pregnancy than herd mates with clinical cure (hazard ratio [HR] = 0.821, 95 % CI = 0.775–0.869; HR = 0.832, 95 % CI = 0.782–0.886; respectively; p < 0.001).

Clinical endometritis

Twice as many cows developed CE after 21 days p. p. if during the first 21 days p. p., they had PM score 3 compared to PM score 1–2 (41.28 % [975/2362] vs. 24.14 % [1510/6256], p < 0.001). Less than 1 % of cows with clinical cure (38/3948) latter developed CE after 21 days p. p. compared to 63.32 % that developed CE of partially cured (1671/2639), and 38.21 % of not cured cows (776/2031; p < 0.001).

The interval from parturition to CE was similar between lactations and between seasons (28.48 ± 0.19, p = 0.12). The interval from PM to CE was almost 1 day longer for 1st lactation cows compared to 2nd and 3 rd plus lactation cows (15.25 ± 0.14 vs. 14.36 ± 0.21 days, p < 0.001).

Cows that had partially cured had tremendously higher chances of developing CE after 21 days p. p. compared to cows that had a clinical cure (OR, 188.39 ± 135.06–262.78; p < 0.0001). Similarly, cows that were not regarded as cured had much higher chanc-



▶ **Fig. 2** Calving to pregnancy interval in grazing dairy cows (n = 7195) from a commercial farm in Argentina experiencing clinical cure to puerperal metritis (PM) (red line, n = 3381), partial cure to PM (green line [almost identical to blue line], n = 2139), or no cure to PM (blue line, n = 1675). Cows with complete clinical cure had shorter calving to pregnancy interval (median, 95 % CI; 109 days, 106–112) than cows with partial cure (122 days, 117–126), and no cure (120 days, 116–125); p < 0.001]. Cows with partial cure or no cure had lower hazard of pregnancy than herd mates with clinical cure (hazard ratio [HR] = 0.82, 95 % CI = 0.77–0.86; HR = 0.83, 95 % CI = 0.78–0.88; respectively; p < 0.001). Source: © R. L. de la Sota.

▶ **Abb. 2** Güstzeit von Milchkühen (n = 7195) mit puerperaler Metritis (PM), diagnostiziert mittels Metricheck, in einem kommerziellen Milchviehbetrieb mit Weidehaltung in Argentinien. Kühe mit klinischer Heilung (rote Linie [fast identisch mit der blauen Linie], n = 3381), klinischer Verbesserung (grüne Linie, n = 2139) oder ohne Heilung (blaue Linie, n = 1675). Kühe mit vollständiger klinischer Heilung hatten kürzere Güstzeiten (Median 95 %-KI; 109 Tage, 106–112) als Kühe mit einer klinischen Verbesserung (122 Tage, 117–126) oder ohne Heilung (120 Tage, 116–125); p < 0,001]. Kühe mit teilweiser oder ohne Heilung hatten eine geringere Wahrscheinlichkeite für eine Trächtigkeit als Tiere mit klinischer Heilung (Hazard Ratio [HR] = 0,82, 95 %-KI = 0,77–0,86; HR = 0,83, 95 %-KI = 0,78–0,88; p < 0,001). Quelle: © R. L. de la Sota.

es of developing CE after 21 days p. p. compared to cows that had a clinical cure (OR, 65.69 ± 47.11–91.61; p < 0.0001) (▶ **Table 5**).

Discussion

To our knowledge, this is the first study to assess the efficacy of ATB usage for the treatment of puerperal metritis and its association with reproductive performance using a big database of cow records from a large grazing dairy herd during 7 years (> 2800 cows). While the use of big data for clinical research has become relatively common in veterinary applied epidemiology [18][23][24], applied veterinary health care [18][23][24], and animal and dairy science [5][20], it has not been the case with clinical trials for the treatment of puerperal metritis and clinical endometritis in dairy production medicine. Most of the randomized clinical trials that assessed the efficacy of ATB usage for the treatment of PM reported in the literature during the last 2 decades have the advantage of comparing an untreated group or positive control group but have the limitation of including a limited number of animals [25]. For example, in a recent meta-analysis of ATB treatment of metritis in dairy cows, from a total of 26 trials that were evaluated, only 7 trials reported cure rates, and 5 from these 7 trials used ceftiofur for treatment of PM [16]. These researchers were able to include in the meta-analysis 828 ceftiofur treated cows and 804 untreated cows and concluded that they were not able to compare different ATB treatments or the efficacy of ATB versus non-ATB drugs to metritis occurrence at the time of reexamination [16]. Conversely, in our study, over 2400 cow records of ATB treatments, clinical cure, milk production, and reproductive efficiency, were retrieved and analyzed to obtain valuable information of efficacy of PM score 3 treatment under field conditions. Probably the major limitation of our study is the lack of non-treated control cows. Still, the main advantage of the study is that the clinical cure rate, the partial cure rate, and no cure rate after reexamination of cows a week later were obtained along with the number of cows that had CE later in lactation and how these events affected the reproductive efficiency of each group.

Diagnosis of PM in grazing systems remains a challenge because fixation the cow to measure the rectal temperature remains the most challenging task of the protocol to abide [3]. This is because cows come only twice a day to be milked at the parlor, and in most dairies, this is the only time were rectal temperature could be measured. Hence many dairies do not measure rectal temperature, and diagnosis of PM is solely based on the type and smell of the vaginal content recovered. In contrast, dairy farms where cows are housed in barns, measurement of rectal temperature can be quickly done after milking when cows are locked in the barns [1][8][13][14][15][26]. One of the significant limitations of our study is that the diagnosis of PM was made solely on the vaginal discharge appearance. However, a recent large study in 45 California dairies showed that 70 % of dairies performed rectal exams for VD evaluation and based systemic ATB administration on the presence of abnormal VD (fetid and non-fetid) regardless of fever (25 %), pyrexia irrespective of the odor of abnormal VD (25 %), fetid VD and pyrexia (2 %), fetid VD (9 %), or fetid VD or pyrexia (9 %) [12]. Also, in a study that investigated how relevant research publications addressed the validity of diagnostic methods for PM, in a selected group of 48 publications out of 259 screened, only 20 % of these publications provided references of the diagnostic techniques used [27]. Furthermore, VD, transrectal palpation and rectal temperature were the 3 methods most often used to diagnose PM, on average more than 2 ways were used per study, and the authors concluded high-quality research was necessary to improve the diagnostic performance of the methods employed [27]. Therefore, it seems that there is no clear advantage of the improvement of PM diagnosis by adding rectal temperature until new scientific data support this recommendation.

The occurrence of PM in this study was like the one reported in previous studies in grazing cows [3] and within the range of variation of those published in housed cows (18 % [4], 18 % [1][28], 20 % [29], 21 % [26], 28 % [30], 36 % [31]). The higher occurrence of PM found in our study could be partially explained because fever was not included as a clinical sign for the diagnosis of PM. Conversely, in one study, it was reported that 58 % of cows with PM did not have a fever [26]. Thus, a great deal of the variation in the occurrence of

▶ **Table 5** Logistic model assessing risk factors for occurrence of clinical endometritis after 21 days postpartum in grazing dairy cows (n = 8618).

▶ **Tab. 5** Logistisches Modell zur Bewertung der Risikofaktoren für das Auftreten einer klinischen Endometritis nach 21 Tagen post partum bei Milchkühen in Weidehaltung (n = 8618).

Effect	Level	Odds ratio	95 % CI	P
Lactation	1	1		0.0099
	2	1.04	0.89–1.21	
	3	1.24	1.07–1.43	
Season	Summer	1		0.5987
	Fall	1.05	0.89–1.24	
	Winter	0.94	0.80–1.11	
	Spring	0.96	0.81–1.14	
PM 3	No	1		0.0914
	Yes	0.89	0.78–1.01	
Cure	Clinical cure	1		< 0.0001
	Partial cure	188.39	135.06–262.78	
	No cure	65.69	47.11–91.61	

95 % CI: 95 % confidence interval; P: probability
PM 3: puerperal metritis present, absent; clinical cure: cow was diagnosed by metricheck with PM score 0; partial cure: cow was diagnosed by metricheck with PM score similar or lower than previous; no cure: cow was diagnosed by metricheck with PM score higher than previous.

PM could be explained by the different diagnostic methods used in the various clinical studies reviewed [16][27].

Similarly, there is a lot of variation in the cure rate reported in different clinical studies, mainly because some use the reduction of rectal temperature below 39.5 °C or 39.2 °C 6–7 days later as a clinical sign for a cure [1], while others use the disappearance of fetid VD or the reduction in the VD score 3 weeks later as a sign of cure [3]; or the combination of both 6–7 days later [9][14]. In our study, 25 % of cows had a complete cure, and 54 % of the cows had a partial cure measured as a change of VD score to healthy or to a no watery brownish fetid VD 1 week later. These results were quite similar those reported in previous studies in grazing dairy cows, however in this study, the endpoint was 1 week, and in the last study was 3 weeks post-treatment (15 %, 52 %) [3]. Collectively, in both studies, the complete cure rate was around 15 %, and the partial cure rate 50 %, however when the cure rate is based solely on change from VD fetid to non-fetid, the total cure rate is 65 %.

The clinical cure based on non-fetid VD with ceftiofur treatments ranged from 26 % to 74 %. The use of rectal temperature alone instead of the disappearance of fetid VD may provide an overestimate of the cure rate. In this study, cows with PM3 had more chances of having CE after 21 days p. p. compared to cows with PM1–2. Similar results were reported previously by Drillich et al. [1], and by Giuliodori et al. [3]. Lima et al. [15] reported that at 32 days p. p., cows that had PM, had 46 % more CE compared to cows that did not have PM.

While most of the clinical studies showed that cows with PM had lower fertility compared to healthy cows, one study did not find differences in fertility between cows with and without PM [15]. Conversely, to our knowledge, there are no studies that show differences in fertility between PM and CM scores; and between cows that had PM and then had a complete cure, partial cure, or regarded as uncured. In this study, cows with a full cure became pregnant 13 days and 11 days earlier than cows that had a partial cure or no cure. Hence improvement in VD from fetid to normal (3 to 0) was related with cows becoming pregnant 13 days earlier. Furthermore, cows with PM score 1 and 2 became pregnant 14 and 12 days earlier than cows with PM3. Hence, the change in the VD score as a clinical indication of cure was proven sensitive and useful to relate it to cow fertility. These results indicate the advantage of using VD over rectal temperature as a clinical feature to show treatment success or failure; and reinforce the concept that rectal temperature alone may overestimate treatment cure [9].

Another important finding from this study was the tremendous impact that PM cure success had on the chances of a cow having a subsequent episode of CE after 21 days p. p. This finding was surprising because the cows with partial cure were the ones with much more chances of having CE than the cows with no cure. Several factors come into play to elucidate the PM cure rate. From the cow's standpoint, avoidance of PM and CE depends mainly on how effective the immune response is to limit the infection of pathogens postpartum [32][33]; from the antimicrobial treatment standpoint, how effective the ATB used is to eliminate the infection [9]; and from the bacteria standpoint, how significant are the shifts in uterine microbiota during the postpartum period [34][35][36], and the appearance of multidrug resistance (MDR) in dairy farms for extensive and reckless use of antimicrobial drugs [37][38]. It is now clear that the availability of calcium and glucose, exposure to elevated concentrations of non-esterified fatty acids or β-hydroxybutyrate, and flux of pro-inflammatory cytokines during the peripartum period may affect some aspects of the neutrophil function and consequently the timing and effectiveness of the immune response [32].

Studies of the uterine microbiota during the postpartum period have clearly shown a shift in microbiota in cows that develop metritis [35]. Cows with PM have increased the abundance of Fusobacteria and Bacteroides, confirming the potential role of these 2 taxa in the pathogenesis of PM [36]. Additionally, metritic cows had a higher abundance of genes for protein transport across the cytoplasmic membrane, type IV bacteria secretion, and resistance to acid stress. Conversely, the uterine microbiota of healthy cows had associated genes for adhesion molecules, bacteriocins, antimicrobial peptides, and tolerance to colicin E2 [36].

Extensive and reckless use of antimicrobial drugs is the basis for the development of MDR in dairy cows [37]. Recent studies in uterine secretions of postpartum dairy cows have isolated *Trueperella* (*T.*) *pyogenes* and *Escherichia* (*E.*) *coli* with genes encoding for MDR and a biofilm virulence factor. *T. pyogenes* was isolated in 42.5 % of samples (17/40), and 35 % of these samples (6/17) were positive for amplicons aadA5 and aadA24-ORF1 in the integron 1, which are associated with sulfadiazine, bacitracin, florfenicol, and ceftiofur resistance (aadA5), and sulfadiazine, bacitracin, penicillin, clindamycin, and erythromycin resistance (aadA24-ORF1). *E. coli* was isolated in 45 % of samples (18/40), and the genes for virulence factor Agn43a and Agn43b were found in 33.3 % of samples (6/18). Furthermore, one cow with PM had had both genes associated with specific drug resistance for *T. pyogenes* and genes of *E. coli* biofilm VF. More recently, the shift of uterine microbiota associated with ATB treatment and the cure of PM in dairy cows was studied [39]. Uterine swabs from ceftiofur-treated, ampicillin-treated, and untreated PM cows were taken on the day of diagnosis and 6 days after treatment to study the changes in uterine microbiota. Bacteroidetes was increased in ceftiofur-treated cows but was not changed in ampicillin-treated and untreated cows; *Porphyromonas* was increased in ceftiofur-treated cows but was not in ampicillin-treated cows; and failure to cure PM was associated with a decrease in the diversity of uterine microbiota and an increase in the relative abundance of *Bacteroides*, *Porphyromonas* and *Fusobacterium* species [39]. It is noteworthy to point out that cows, that after calving progress to PM, have a shift in uterine microbiota, decreasing the abundance of Proteobacteria and increasing the abundance of Bacteroidetes and Fusobacteria [39]. One recent study was aimed to investigate the prevalence of extended-spectrum β-lactamase (ESBL) producing bacteria in uterine samples of cows with PM. The results from this study showed that cows with PM had a high percentage of ESBL producing intrauterine pathogenic *E. coli* with multidrug resistance to 29 ATB classes, including ceftiofur [40].

Finally, in a recent study, fecal samples from dairy cull cows form California dairies were obtained to study the association between herd management practices and AMR in *Salmonella* spp. [38]. In 12 % of the fecal samples, an MDR *Salmonella* spp. was isolated, and the 3 most common drug classes which isolates were resistant to, were tetracycline (39 %) ampicillin (18 %), and cephalosporins (10 %). Furthermore, at a cow-level, prior treatment with MDR as the reason for culling was associated with higher odds of isolating MDR resistant Salmonella [38].

Collectively, these studies support the idea that the response to ceftiofur treatment in PM is very variable. For some practitioners, a case remission is no fever, for others is the appearance of a non-fetid VD, for others appearance of a normal VD, and others no fever and appearance of a non-fetid VD. For example, in this study, the cure rate could be of 25 % (normal VD) or 78 % (non-fetid VD). Including in the group of cured cows those that had a change from PM fetid VD to CM no-fetid VD maybe not appropriate because they are no cure, and this is reflected by the difference in days open between both groups. Therefore, to accurately assess the efficacy of ATB treatment, the clinical response to measure should be the restoration of a normal VD, which, based on the results of this study, is followed by higher fertility.

When PM is compared to other postpartum diseases in dairy cows like clinical mastitis, 2 major differences in treatment practices strikeout, the first difference is that most of PM clinical trials measure clinical cure rate and fertility but do not measure bacteriological cure. The second difference is that, whereas in clinical mastitis in farm bacteriological culture is a standard procedure used to decide on case treatment, in PM is not. In the past, we have studied the effect of a selective ATB treatment strategy based on a quick bacteriological on-farm test (Petrifilm, 3 M Corp., St. Paul, MN, USA) compared with the conventional ATB treatment of all cows having CE [41]. The selective ATB treatment strategy based on the outcome of the Petrifilm test reduced the number of required treatments (57 %) and it maintained similar efficacy in terms of clinical cure and reproductive performance as the conventional ATB treatment of all endometritic cows [41].

CONCLUSION FOR PRACTICE

Big data of treatment records of PM in dairy farms can be used in retrospective studies to respond to clinical questions about cure rate, risk factors, and benchmark demographics, treatments, and productive and reproductive efficiency of treated and untreated animals.
After ceftiofur treatment, 3 out 4 cows were cured when measured by disappearance of fetid VD but only 1 in 4 cows had clinical cure when measured appearance of a clear VD.
The cows that remained with PM1–2 had more chances of having CE after 21 days p. p. and had more days open than cows with clear normal VD.
Cure rate measured by return to a clear VD is low, and these could be explained by a lack of effectiveness of the cow's immune response the infection of pathogens during the postpartum period, by how effective the ATB used are to eliminate the infection, by how significant are the shifts in uterine microbiota during the postpartum period, and by the appearance of AMR in dairy farms due to extensive and reckless use of antimicrobial drugs.
There is a need to start to conduct bacteriological culture or a quick bacteriological on-farm test to select cows before ceftiofur treatment to improve the cure rate, reduce AMR and reduce ATB usage.

Conflict of interest

The authors confirm that they do not have any conflict of interest.

Dedication

We dedicate this article to Univ. Prof. Dr. Wolfgang Heuwieser upon his 65th birthday.

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