BACKGROUND

Bacterial infection of synovial structures, such as joints, tendon sheaths and bursae, are common and dreaded complications in horses. It is generally accepted that synovial sepsis may be life-threatening or career-ending for the horse (McIlwraith 2002). Diagnosis and treatment are best taken care of in hospital facilities, because of the complexity of the therapeutic interventions, which generally are very costly (40- 50.000 SEK and up). Despite intensive treatment, the outcome may vary - from chronic synovial infection with complications as painful arthroses, ankylosis or death, to complete resolution of the condition.

Bacteria may gain access to the synovial structure by haematogenous spread, via traumatic wounds or via iatrogenic accidents. While the first route is almost confined to foals, traumatic wounds on the limbs of horses relatively often may involve on or more joints and other synovial structures. During the wounding process, inoculation of foreign material and bacteria takes place and infectious material is introduced directly into the synovial structure or close enough to these to later invade the synovial structure. Iatrogenic inoculation of bacteria is relatively uncommon, but is seen especially during intra-articular treatment of otherwise non-septic joints, or during arthroscopic surgery (Lapointe et al. 1992; Bertone 1996). After contamination and an unknown period of time, some of the introduced bacteria may overcome the host defense and establish an infection. This infection and the response to it by the horse, induces a number of inflammatory reactions, which are designed to eliminate the bacteria, but also actually may destroy vital parts of the joint, as the cartilage. Factors involved may be matrix metalloproteases, free radicals prostaglandins and some cytokines, as IL1,6 and 15 (Henningsson et al. 2012, McIlwratih 2002). Cartilage has a limited capacity for repair, and therefore cartilage damage is often associated to development of chronic joint disease. Also septic inflammation often leaves “scarring” in the joint or the tendon sheath, fx in the form of adherence formation, which can be athletically debilitating. Therefore, the earlier such establishment of an infection can be determined, the better an efficient treatment can initiated, and the better the prognosis ifor full restoration of the synovial structure can be expected.

The clinical diagnosis “septic synovitis” is often made on the basis of the classical cardinal signs in the region: Swelling, pain, redness, heat and lameness. Synoviocentesis and analysis of synovia will yield more information: Loss of viscosity, discoloration, increased protein concentration (> 25 g/L) and presence of white cell count > 30 x 109/L, with a percentage of more than 90 % of neutrophils, are highly indicative of a septic synovitis. (McIlwraith 2002). However, the ultimate diagnosis is based on microbiological analysis of bacterial strain and its antibiotic sensitivity pattern in synovia.

Survival and performance ranges after synovial sepsis are very broad, as communicated in the literature. In practice, these ranges will complicate the communication and the advices from the clinician to the client, who might feel that the treatment outcome is a lottery. It is also obvious that yet undescribed factors must be important for the outcome.

We hoped to address three such possible factors in this project.

First; the time factor. IOt is widely accepted that the single most important factor for a good prognosis is that the causative microorganism is isolated, in order to guide the correct treatment (E.g McIlwraith 2002, Baxter 2004). It is known that cartilage of equine joint can be destroyed within 24 hours after infection, and formation of fibrous adherences in a tendon sheath can invalidate the horse, despite the resolution of the infection (Smith et al. 1987). In contrast to this, a recent study from Australia (Walmsley et al. 2011) has shown that longer duration from contamination to treatment did not influence the prognosis. Most of horses in the Walmsley study would in Sweden have been classified as chronic infections and the case-material would therefore not be comparable to the typical Swedish population, were horses tend to be referred to a hospital immediately if a penetrating wound is suspected. It is also important to acknowledge, that most of studies on prognosis are retrospective and therefore a number of factors varies considerably, as for example time from contamination to diagnosis. Considerable controversy therefore still exist on how the timely treatment influences the survival rates.

Time from contamination to microbiological report/clinical action depends on the available laboratory and methods. Traditionally, isolation of bacteria in synovial fluid involves preculturing of the bacteria and subsequent phenotyping, based on fx fermentation. Isolation of bacteria from synovial fluid is however often disappointing, because a high number of false negatives, probably due to factors as phagocytosis of the bacteria, use of antibiosis, and/or host related defense mechanisms. One study showed that only 38% of truly positive synovial samples could be cultured on agar. When blood culture enrichment medias were used, the recovery of isolate increased to 78% (Dumoulin et al. 2010). Most laboratories would need in the best case 48 hours to perform this conventional phenotyping and to this should be added to the logistics and the delivery time for the synovial sample. It would therefore be of utmost relevance to identify and test the newly emerged method used in human clinical microbiology such as MALDI TOF for the ability to fast detection of bacteria in synovial fluid.

MALDI-TOF (matrix-assisted laser desorption/ ionization – time of flight) belong to the family of mass spectrophotometry and ithe technique is currently used in microbiology, to detect the "fingerprints" of various bacteria. MALDI-TOF-MS is a rapid, precise, and cost-effective method for identification of intact bacteria, compared to conventional phenotypic techniques or molecular biology. Furthermore, it allows identification of bacteria directly from a clinical sample.

The technique is described further in a recent review by Carbonelle et al. (2011). To our knowledge, MALDI TOF has not yet been used for synovial microbiological diagnosis in veterinary medicine. It is therefore of great interest to investigate the potential use of MALDI TOF in equine rapid diagnosis of synovial infection.

Secondly; the role of microbial diagnosis. The outcome after synovial sepsis is believed to be related to the species and genus of the infecting bacteria. Older north-american literature states that the most common bacteria involved in synovial sepsis are aerobes or facultative anaerobes, and the most common bacteria genus is Enterobacteriacaea, followed by Streptococcus and Staphylococcus (McIlwraith 2002). Two more recent and European studies have found other proportions. A Belgian study showed that out of 75 culture positive samples, Staphylococcus aureus could be cultured from 13 %, Streptococcus sp. from 15% and Bacillus from 12 % of cases admitted to the Hospital. All together Gram positive bacteria accounted for 73% of the positive cultures, while 13% of the isolated were Gram negative (Dumoulin et al. 2010). An English study cultured bacteria form 206 horses with septic synovitis and found Staphylococcus aureus in 34% , Streptococcus in 11 %, and mixed growth in 11% of these cases (Taylor 2010). The aforementioned studies were not designed for epidemiological purposes, and therefore the data cannot be generalized without great caution. However, it seems as if there are no rules of thumbs regarding the expected microbiological finding in synovial structures. The study by Taylor et al. (2010) further showed that if a synovial sample culture is positive, the prognosis will be negatively affected and the prognosis will be further aggravated if the infecting agent is a Staphylococcus . This was however not the case in a similar study by Schneider et al. 1992. Controversy therefore exists on the prevalence of the different microbiological infections and whether some bacteria are associated with poorer prognosis for short term survival and/or full athletic restitution. No such published data exist for Swedish horses admitted to Swedish hospitals.

Thirdly, the potential role of other factors. It is quite likely, as is the case for other infections, that a number of host related factors, such as co-morbidity, immune status, age and gender has a relation to the outcome of synovial contamination during a wounding. Most clinical studies cited in the literature have been retrospective studies, where only a few of these parameters can be retrieved in a reliable manner from the record. A study of prognostic indicators for horses with synovial infections by Walmsley et al. (2011) concluded that decreased survival was only related to evidence of bone and tendon involvement in a wound. Whether this is the case for Swedish horses, remains to be investigated.

Aims of the study were:

1. To compare the results of conventional bacterial phenotyping and MALDI-TOF detection regarding accuracy of typing and time to detection.
2. To investigate the possible relations between MALDI-TOF typing of bacteria and the commonly evaluated synovial fluid parameters Total Protein, White Cell Count, Differential Count, Viscosity and Colour and clinical findings, such as co-morbidity and lameness.
3. To describe the pathogens involved in septic synovitis and their pattern of antibiotic resistance in horses admitted to large Swedish equine hospitals.
4. To describe the rates of survival and return to athletic performance, and the possible relation to synovial pathogen and time of contamination in a Swedish Hospital setting.

The sampling periods started in February 2013 and has continued to June 2017. We have analysed our data on a continuing basis, but will deliver final results for publications during the autumn 2017. Sabrina Skov Hansen UDS has been added to the study group 2016, when she started her surgical ECVS residency. Frederick Willett, veterinär, Evidensia Specialisthästsjukhuset Helsingborg, was added to the study group 2015. In 2014 Drs FL Winberg and Tamas Toth left the study group.

Material and Methods

Design:

Prospectively conducted descriptive clinical study without intervention performed in one university hospital and in one specialised equine hospital with follow up after discharge from hospital.

Horses:

Horses and foals (n=86 per January 2017) with suspected synovial infection admitted to the SLU University Hospital (UDS) from January 1st 2013 to June 2017 and Evidensia Specialisthästsjukhuset Helsingborg from January 2015 to June 2017.

Study protocol

Case selection

Horses were remitted to the UDS or Helsingborg Evidensia Equine Specialist Hospital from February 2013 to June 2017. When a horse was enrolled in the study a pre-assembled bag containing all disposables, owner consent form, protocol schemes and remises were picked in the examination room. The owner was then informed that the sampling of synovia is a regular part of the clinical diagnosis, and asked for consent of the following: 1) The remaining synovia will used for research, 2) The horse may be subject to a haematological/biochemical investigations.

After having obtained informed consent, performed the relevant synoviocentesis and cared for the horse, synovial assessment was performed.

Figur 1. Veterinarian Sören Ladefoged samples a horse for MALDI TOF

Handling of synovia

Evaluation of the synovia was performed as fast after recovery as possible, and comprised visual inspection (colour, debris, transparence and viscosity) and refractometry (grams of protein per L). Synovia was aliquoted and shipped for traditional and MALDI TOF microbiological examination including antimicrobial resistance pattern; and for cytological examination at the UDS laboratory. Blood samples were drawn, spinned and stored at minus 80°C together with remaining synovia, if available.

Figur 2. Orange synovia indicating infection or blood contamination?

Synovia and serum were sent for analysis of acute phase reactants. These data are still pending.

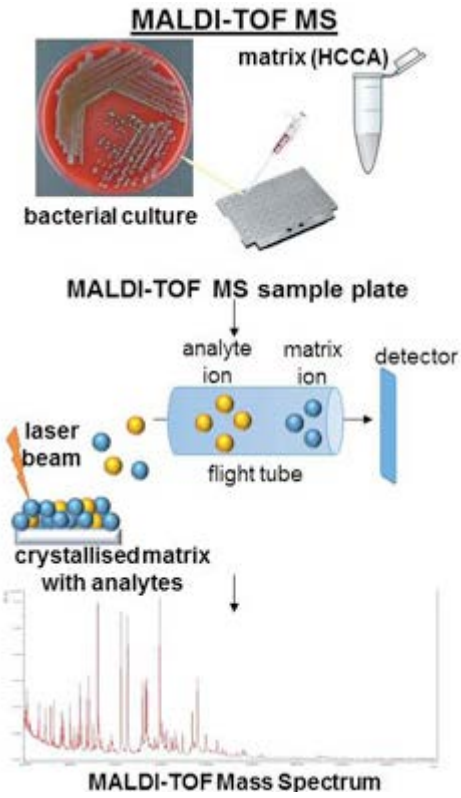
Medical records and interviews.

The medical records of all horses were screened for clinical data on age, gender, affected joint(s), degree of lameness, cause of suspected joint infection; periarticular joint swelling; effusion and blood parameters when available. Follow-up telephone interviews on performance were performed 12 months after discharge from the hospital. We have not yet finished the interview part.

All results were entered into an Excel sheet, with patient name and hospital journal number as ID entry.

MALDI-TOF and conventional bacterial typing

The principle of the MALDI TOF method used is described in detail elsewhere, but briefly the extracted sediment from the enrichment flask is placed on a steel plate and covered by a special matrix. The steel sample plate is then placed into the Maldi typer and irradiated with in a pulsed laser beam. The laser beams energy interacts with the matrix and ionizes any present bacterial ribosomal proteins. The ionized proteins travel through a voltage field in a vacuum chamber – a flight tube. Any present ionized proteins are detected and give rise to specific mass-spectra. The mass-spectra can then be used as a microbiological fingerprint and by comparing the acquired mass-spectra with mass-spectra stored in a database allowing bacteria from the analysed synovia to be detected and identified (Figure 3). MALDI-TOF MS has proven reliable and rapid and has the ability to determine the identity of an isolate from culture in a matter of minutes rather than the hours or days required by more traditional methods. Methods are emerging that extend the utility of MALDI-TOF MS to include bacterial identification directly from clinical samples as well as providing timely information regarding antibiotic resistance and typing of different micro-organisms.



Figur 3. Principles of MALDI TOF (http://www.jbmethods.org/public/journals/1/cover_article_125_en_US.jpg)

MALDI TOF and conventional bacterial typing was performed by Dr Elisabeth Bagge, Statens Veterinärmedicinska Anstalt. Bacteria from joints have to pre-grown in enriched media, before a sediment can be obtained and smeared onto the sampling plate. Synovia was injected into to blood enrichment flasks manufactured at the National Veterinary Institute Uppsala, Sweden. The blood enrichment flasks was incubated at 37° C and after varying time of enrichment (i.e 4h, 8

h , 24 h and 48 h) approximately 1 ml of the enrichment broth was investigated for putative growth of bacteria by MALDI-TOF technique , using mass spectrometry technology. Analyses were performed on a Bruker Maldi typer (Microflex™) from Bruker Daltonics connected to a PC using the software Plexicontrol and the database Biotyper 3.0.

Preliminary testing of performance of the MALDI TOF system in synovia.
Before testing clinical cases, a pilot study on the recovery of bacteria from synovia after cultivating in enriched media was conducted. After spiking of fresh synovia with between 10 and 100 bacteria of the most relevant equine synovial pathogens, the spiked synovial samples were transferred to a SVA blood culture flask. Samples for MALDI-TOF was taken out and analyzed at 2, 6, 12 and 24 hours. *Staphylococcus* could be detected within 12 hours of inoculation and the methods generally seemed to work well with synovia.

Preliminary testing of manual analysis versus automated analysis and effect of culture media.
During the study period, the methodology of MALDI TOF changed significantly; new equipment automatically analyse the samples and new growth media are used for this machine.
We therefore conducted a study with the purpose to compare old, biphasic bottles that are analyzed manually with new bottles analyzed by machine.

Before the experiment was started, a pilot study was conducted where four aerobic and one anaerobic bacteria were tested to see whether the bottles itself benefited or disadvantaged for the respective bacteria. The five bacteria were *Streptococcus zooepidemicus*, *Staphylococcus aureus*, *Eschericha coli*, *Actinobacillus suislike* and *Fusobacterium necrophorum*. There was no big difference between the different bottles. Streptococcus zooepidemicus, S. aureus and E. coli, increased from $\log10^{2}$ to $\log10^{8}$ during incubation in both bottles and A. suislike increased from $\log10^{4}$ to $\log10^{8}$. Fusobacterium necrophorum increased from $\log10^{3}$ to $\log10^{7}$.

Samples from horse joints were taken from clinically cases. Recommended amount of sample was six mL, but also five mL was included in the study. One mL of synovia was injected into aerobic and anaerobic blood culture bottles, both biphasic blood culture bottles and Bact-Alert bottles. The biphasic bottles were manually read once a day and at least in seven days. The Bact-Alert bottles were read by machine and grown a total of seven days.

The biphasic bottles
When the bottles arrived at the National Veterinary Institute (NVI), they were directly analysed by Matrix Assisted Laser Desorption Ionization Time of Flight mass spectrometry (MALDI-TOF MS), (Bruker Daltonics Microflex, MALDI Biotyper, Bremen, Germany) according to manufactures standard laboratory procedure. The analysis was repeated after one day. At both occasions, a cultivation has also been done on horse blood agar and bromecresol lactosepurpur agar. The anaerobic bottles were also cultured on Fastidious Anaerobic agar.
Bottles were then incubated until any growth could be shown or at least for seven days. Even in these cases the bottles were grown on horse blood agar and bromecresol lactosepurpur agar. The anaerobic bottles were also cultured on Fastidious Anaerobic agar. A MALDI-TOF score of 1,7-2 were regarded as significant for detection of genus. A score >2 regarded as significant on species level.

The Bact-Alert bottles.
When the bottles arrived at the SVA, they were immediately incubated into the machine. If the machine alarmed, the bottles were removed and cultured on horse blood agar and bromecresol lactosepurpur agar. The anaerobic bottles were also cultured on Fastidious Anaerobic agar.

Relevant findings were tested by antimicrobial susceptibility test if possible.

Data management and analysis
Descriptive statistics were carried out for each type of pathogen. The variables Total Protein, White Cell Count, Neutrophil Count, Viscosity and Colour, co-morbidity and lameness were entered as

explanatory variables into a logistic regression model with backward elimination, with MALDI TOF positive results as response. Using simple descriptive statistics from the both conventional and MALDI TOF data, the first description of synovial pathogens and their antibiotic sensitivity pattern will be available in Swedish Hospital setting. Short term survival was described as the proportion of horses included in the study that leaves the hospital. Long term follow up was described as the proportion of horses still alive one year after discharge, as well as the proportion of horses that returned to expected or prior athletic performance.

Ethical permission
Ethical permission was obtained from Regional Ethical Review Board, Sweden (C414/12). The permission was later extended to include sampling sites Helsingborg Djursjukhus och Strömsholm Djursjukhus.

A brochure explaining the study and the purposes was given to relevant horse owners as informed consent was one of the inclusion criteria in the study. The study was generally welcomed and only few horses were lost to the study because of lacking owners consent.

Results

A total of 86 horses were sampled. Due to an error in the remiss MaldiTOF was only performed in the UDS obtained samples (N=41).

Causes of the synovial infection (prel. data) were haematogenous spread (foals) 8%, iatrogenic injection infections 5 %, post-surgical infections 3 % and the remaining 86% could be related to wounds of which 62% had verified penetration, with 3 % stab wounds and 3 % with a foreign body. The fetlock and tarsal joints were the most commonly affected structures, with respectively accounting for 36% and 27% of the wounds.

Microbiological findings. The bacteria found in synovia by both traditional and MaldiTOF when available were: *Actinobacillus equuli ssp. Equuli, Actinobacillus equuli subsp. Haemolyticus, Actinobacillus suis, Aerococcus viridians, Arthrobacter gandavensis, Bacillus cereus Dichelobacter nodosus, Escherichia coli, Staphylococcus capitis ssp urealyticus, Strep. Equi sp., Streptococcus equi ssp zooepidemicus* and *Streptococcus gallinaceus.*

Of the suspected infected joints, 31 % were positive during a traditional culture. The MALDI-TOF examinations were positive in all of these positive cultures but in none of the negative cultures.

Antimicrobial resistance patterns: We have screened all records from 2010 to 2016, but analysis and validation of the data are pending. To be finished in spring 2018.

Discussion

MALDI TOF. Our preliminary results show that MALDI TOF indeed can be used to detect bacteria in synovia, but only after culturing for 24 hours in suitable media and subsequent extraction. Because this is a manual and tideous process, the fastness of the system probably cannot be entirely exploited with the present system. Practical obstacles were encountered by receiving synovial samples shipped by post. The incubation time and the temperature condition in the media was uncertain and samples that should reach SVA in time to be processed before the weekend should be shipped at the latest Wednesday from Helsingborg. Logistics thus were complicated and in none of the cases we used the otherwise very fast MALDI TOF answer for decision making in the clinic. Therefore we will not be able to document any beneficial effect of the MALDI TOF for our clinical cases. This does not mean that the MALDI TOF method is not valid, we actually obtained reliable and fast result when

circumstances were optimal, indicating that the MALDI-TOF equipment probably should be located in-house in order to the desired gain in time.

The two methods identified the same bacteria, but when timing of sampling and laboratory capacity was optimal, the MALDI TOF could deliver a result within 24 hours. In our preliminary material, 69% of the samples were negative in both methods, thus MALD TOF did not detect bacteria in samples that were negative in the conventional method. This is somewhat disappointing, as we expeted that the MALD TOF would identify more infections than the traditional methods.

Clinical data. Neither degree of lameness, nor macroscopic data such as turbidity or colour of the synovia could be associated with infection or bacteria involved. In our study, the most reliable and fastest parameter for joint infection was still the presence of high levels of recruited polymorhnucleated cells in the synovia. However few veterinarians performs synovial cytology, even if that is simple and fast. It could therefore be speculated whether inexpensive and simple biochemical tests would be worth investigating in synovial fluid of the horse. One example from the human clinic is *adenosine deaminase*, where the concentrations correlates closely to neutrophil count.

Conclusions
In conclusion, the MALDI TOF system can reliably analyze synovial samples from horses, and yields results at least as sensitive as the old system, but potentially much faster. However, until we have logistics that can exploit the potential fastness of the system, clinicians should still rely on treatments that contain joint lavage, use of broad spectrum antibiotic and follow up based on synovial white blood cell differential count.

PLAN FOR COMMUNICATION WITH STAKEHOLDERS/END USERS:
Our results will also be presented at international surgical and/or orthopaedic conferences.

Kommunikations-kanal	**Huvudsakliga mottagare**	**Tidsplan för förväntad leverans av del- och slutresultat**
2018: The Nordic Equine Veterinary Conference, NEVC, 9-11 Feb. 2018	Forskarvärden	*Does synovial colour and turbidity predict bacterial culture results?* Sabrina S. Hansen, Elisabeth Bagge, John Pringle and Pia H. Andersen. ***Published*** *as a conference abstract.*
Ridsport/Hästsport-tidning	Hästsporten	*2018* autumn (Andersen and Skov Hansen). Interview on joint infections: When to call the veterinarian, and what will she actually do and why.
Veterinärmötet *Deadline for submission of abstract: 1.juni 2018*	Veterinärkåren	2018 november: S. Skov Hansen et al: *Horse side testing as indicators of joint infection.*
American Association of Equine Practitioners. Dec 2018. How to session. *Deadline for abstract: March 15. 2018*	Forskervärlden	*Does synovial colour and turbidity predict bacterial culture results?* Sabrina S. Hansen, Fredrik Willett, John Pringle and Pia H. Andersen. As the NECV presention, but including data from one more hospital.
Relevant vetenskaplig tidsskrift	Forskarvärlden	2018 or later to be submitted to Equine Veterinary Journal: *Title "Microbiological diagnosis of equine synovial infections by MALDI TOF"* *We have discussed a manuscript submission with the relevant journals and pointed out the weaknesses regarding the sample sizes and the long period of*

		sampling. As expected and in accordance with the sample size proposed in the original project, it is doubtful whether a "negative" result can be published as it is. We have therefore decided to continue the sampling, in order not to lose the valuable data already collected and then publish ion. "NHS" will of course be mentioned as main sponsor.
Svensk Veterinärtidning	Veterinärkåren	2018 (Sabina Skov Hansen, Frederick Willett, Pia Haubro Andersen, John Pringle and Elisabeth Bagge). *Title: Synovial infections in two large Swedish horse hospitals 2010-2016. A retrospective study of microbiological typing and antibiotic sensitivity.*
Hästsektionens årsmöte 2019 *Deadline for submission of abstract:*	Svenska hästveterinärer	2019 Sabrina S. Hansen et al: *Is MALDI TOF really faster and more precise than clinical signs in diagnosing synovial infection? Preliminary data from 36 (+) cases of suspected synovial infection.*

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