TITLE: Spontaneous Septic Arthritis of Canine Elbows: Twenty-One Cases

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Manuscript Title:

Spontaneous Septic Arthritis of Canine Elbows: 21 dogs

Objective: To provide information on the clinical features, diagnosis and treatment and associated risk factors of spontaneous septic elbow arthritis in the dog.

Methods: Medical records from two referral institutions between March 2007 – June 2015 were searched for cases of spontaneous septic elbow arthritis with a diagnosis based on clinical signs, arthrocentesis, cytological and microbiological analysis of elbow joint synovial fluid, radiography, and outcome following treatment.

Results: 21 cases of septic arthritis were identified. Pre-existing chronic osteoarthritis was present in 93% of elbows for which diagnostic imaging was available. Although all cases had increased neutrophil count on synovial fluid cytology, culture was only positive in 52.3% of cases. Despite initial improvement in lameness scores (pre-treatment 7.5/10 (range 1-10) vs post-treatment 3/10 (range 1-5)), 92% had residual long term lameness based on clinical records and owner follow-up. Recurrence of infection was noted in 25% of elbows for which long term (>8 weeks) follow-up was available. There was an acute mortality rate of 2/21 (10%) associated with severe systemic sepsis.

Clinical Significance: Septic arthritis, even in the absence of pyrexia, should be considered as a major differential diagnosis in middle aged, large breed dogs, with pre-existing elbow arthritis, that suffer an acute onset lameness, with elbow joint effusion and discomfort. Antibiotic therapy alone is effective for treatment with high initial response rates of 94%. Chronic lameness post-treatment was common, and a high rate of recurrence was seen with 25% of dogs suffering more than one episode.

Introduction:

Septic arthritis is considered an uncommon condition that can significantly impact the quality of a dog's life (1). Septic arthritis is an active joint infection, which is usually bacterial in origin and results in an acute inflammation of the joint, with swelling, pain and lameness (1, 2). Bacterial contamination of the elbow may arise from direct inoculation (at surgery or related to trauma), or by the extension of local infections or by haematogenous localisation (3). The term spontaneous is used in this report to describe infections in which there has been no known recent surgical or traumatic episode to the afflicted joint and the infection is presumed haematogenous in origin (4). The majority of bacterial septic arthritides manifest as a monoarthropathy, and may be either acute or chronic in onset (3). A clear joint predilection of septic arthritis in dogs has not been established for cases of spontaneous infection. In the veterinary literature, in which surgical related infection is variably included, the stifle is most commonly affected 16.1 – 73.7%, with the elbow showing variable predilection rates of 12.9 – 38.7% (3, 5-7). Pre-existing joint diseases, such as osteoarthritis, and concurrent medical conditions (diabetes mellitus, skin disease, urinary tract infection, prosthetic joints) may predispose the joint to opportunistic infection (2, 8). Septic arthritis more often affects larger breeds, with an apparent over-representation of males (3, 5-7). The definitive diagnosis of septic arthritis has traditionally relied on the identification of bacteria from the affected joint by synovial fluid or synovial membrane culture. The difficulty is that bacterial culture is frequently unsuccessful and diagnosis must often be based on a degree of suspicion (1, 9). Often a presumptive diagnosis of bacterial infective arthritis is made where synovial fluid from a monoarthropathy shows very high nucleated cell counts (>50 x 10^9 cells/ml), predominantly polymorphonuclear cells and/or the presence of intracellular bacteria on cytology (1).

Despite several retrospective articles on the subject of septic arthritis, there is limited information on the signalment, treatment success, recurrence and long term outcome of cases

of septic arthritis in the elbow joint of dogs that have not had recent surgery (3 – 7). This study aimed to review the current literature on septic arthritis and describe cases of septic arthritis including the history, presenting complaint, underlying disease state, response to treatment and outcome.

Materials and Methods:

The clinical records database of two tertiary-level referral institutions were searched for cases of septic arthritis or bacterial infective arthritis that had been diagnosed between March 2007 and June 2015 to determine relative joint prevalence. Cases identified for septic arthritis were then further stratified to identify cases of spontaneous septic arthritis of the elbow. Inclusion criteria were the diagnosis of a monoarthopathy, where analysis of either the synovial fluid or membranes was consistent with septic arthritis, and there was no recent surgery of the elbow joint within one month of presentation or one year if implants were placed (3, 10). Analysis of synovial fluid or synovium was required to fulfil one or more of the following criteria; highly cellular appearance observed subjectively on a direct smear, >40% neutrophil population in the synovial fluid; a total nucleated cell count of more than 50.0×10^9 cells/ml; a positive synovial fluid or membrane bacterial culture (5, 11).

The medical records, physical examination and recent haematology and blood biochemistry results from cases were reviewed. Synovial fluid samples had been obtained from the affected joint by percutaneous arthrocentesis following aseptic preparation in anaesthetised or deeply sedated patients (12). Synovial fluid samples were submitted for culture and sensitivity after innoculation into blood culture media. Culture was performed as previously described (3)

Lameness of the affected limb was extrapolated from clinical records of patients as assessed and recorded by either RCVS or ECVS board certified veterinarians pre- and post- treatment using a numerical scoring system (13, 30). Because of the variability of recorded information between patient and across the time period of the study the following grouping was defined:

- 0 – Sound, no lameness
- 1 – Occasionally shifts weight off affected limb
- 2 - Mild lameness at a slow trot, none whilst walking
- 3 – Mild lameness visible whilst walking
- 4 – Obvious lameness whilst walking, but places the foot whilst standing
- 4-7 - Moderate lameness in degrees of severity
- 8 - Severe lameness
- 9 – Places toe when standing, carries limb when trotting
- 10 – Non weight bearing

When imaging studies of the elbow was available the plain radiography and CT scans of the elbow joints were reviewed by two of the authors. Images were assessed for the presence of osteophytes; at the anconeal process, medial and lateral epicondyles, and radial head; ununited anconeal process (UAP), fragmented medial coronoid process (fMCP), incomplete ossification of the humeral condyles (IOHC) and humeral condyle osteochondrosis dissecans (hOCD). A global assessment of osteoarthritis (OA) was given; none (no osteophytes), mild (small numbers of osteophytes less than 1 mm in size, moderate (osteophytes at multiple sites, 1-2mm) or severe (osteophytes larger than 2mm) following concensus between the two authors (5).

Short term (defined as a period less than eight weeks) outcome, was recorded as clinically *successful* where there was a return to the level of ambulation prior to recent episodes of lameness, clinically *unsuccessful* if there was continued lameness at or to a greater degree than prior to intervention but with resolution of infection; and as *failed* if the synovial fluid cytology was not consistent with resolution of the bacterial infection at the last recorded treatment (4, 14). Long term outcome (>8 weeks) was reviewed for ongoing lameness, recurrence of infection or further surgical intervention and was evaluated by both owner telephone call and assessment of clinical records where available.

Statistical analysis was performed by one of the authors using a statistical software package (SPSS Stat, Version 2.2, IBM Corp). Normality of data was assessed by a Shapiro-Wilk's test and presented as mean +/- standard deviation when parametric and median +/- range when non-parametric. The project was ethically reviewed (URN 2015 1359) by the respective institutional Research Ethical Review Boards

Results:

Twenty-seven cases of septic arthritis of the elbow joint were initially identified during the data collection period. Five elbows were excluded due to a history of recent surgery involving the septic elbow. One case was excluded based on repeat synovial fluid analysis consistent with an immune-mediated process (polyarthropathy with non-degenerate neutrophils on synovial fluid analysis), resulting in a total of 21 elbows meeting the inclusion criteria for spontaneous septic arthritis, (summary of case details is provided in Appendix 1). Breeds included Labrador Retrievers (n=11), and one each of English Springer Spaniel, Cross Breed, Munsterlander, Golden Retriever, Bull Mastiff, Rottweiler, German Shepherd, Saint Bernard, Cavalier King Charles Spaniel (CKCS), Patterdale Terrier and Staffordshire Bull Terrier (SBT). The mean

age of dogs in this report was 6.8 years +/- 2.3. The median body weight was 35.5 kg (9 – 83 kg). The right elbow joint was involved in 10/21 cases, left in 9/21 and 2/21 cases were bilateral.

Nine dogs (43%) were receiving treatment for concurrent medical conditions at the time of initial presentation; idiopathic epilepsy (n=3), diabetes mellitus (n=3), urinary tract infection (n=2), hypothyroidism (n=1), acute lymphoblastic leukaemia (ALL) (n=1), paraprostatic cyst (n=1) and anal furunculosis (n=1). Two of these dogs had more than one concurrent disease. Immunosuppressive therapy was being used in two cases; the patient with ALL was receiving a chemotherapy protocol combining doxorubicin[a] vincristine[b], cyclophosphamide[c] and prednisolone[d] and the anal furunculosis case was receiving cyclosporine[e]

A history of prior orthopaedic surgery was identified in 11 cases that met our prior inclusion criteria. Three of these had a history of surgery at a site distant to the infected elbow, (tibial plateua levelling osteotomy (TPLO) with implants in place). The remaining eight had a history of surgery on the septic elbow joint; however it was outside of the time frame for exclusion as a surgical site infection. Seven did not have implants (elbow arthroscopy (n=5, 3-8 years prior), bilateral forelimb angular limb deformity and ulnar osteotomy (n= 1, 9 years prior), bilateral elbow hygroma (n=1, 2 years prior), the eight case had a stainless steel transcondylar lag screw for incomplete ossification of the humeral condyles (, 1 year prior). The median time since prior surgery was three years (range: two months to eight years). Of the three cases that had a TPLO procedure performed, two had surgery within two month of presentation for forelimb lameness. Both of these cases had evidence of surgical site infection of the distant original surgical site suggesting the possibility of a haematogenous spread to the elbow.

At presentation, physical examination findings included joint effusion (n=21), pain upon manipulation of the affected joint (n=21), lethargy (n=8), muscle atrophy (n=6), regional lymphadenopathy (n=5), pyrexia (>39.2°C n=5), systemic leucocytosis (n=6). Sixteen cases were referred as an emergency consultation due to an acute deterioration in lameness. Of these 16 cases, twelve had a chronic (>2 month) history of forelimb lameness prior to deterioration. The remaining five dogs were presented for an investigation of chronic lameness through routine referral consultation. The duration of deterioration in clinical signs in all dogs was median 4.5 days (1 – 120 days) and a lameness score on presentation was median 7.5/10 (range 1-10). The group of dogs (n=5) presenting for investigation of chronic forelimb lameness had clinical signs of greater than two months and lameness score of median 5/10 (range 1-10). Routine haematology and serum biochemical results were available for 13/21 cases. A leucocytosis was present in 4/13 cases with neutrophilia in 5/13. A thrombocytopenia (<150 $x10^9$/L) was present in three cases; two of which had concurrent neutropenia (<3 $x10^9$/L). Of these two cases; one (Case 14) was receiving chemotherapy for ALL; and the other (Case 15) was euthanatised due to clinical deterioration and signs of suspected sepsis (pyrexia, tachycardia, neutropenia) (29). Alkaline phosphatase was elevated in three dogs.

Imaging available for evaluation included orthogonal radiographs in six and computed tomography (CT) of the elbow joint in nine elbows. Osteophytosis was present in 14/15 elbows, fMCP was seen in nine elbows, UAP in one, IOHC in one and hOCD in two. Global OA assessment was severe 11/15, moderate 1/15, mild 2/15 and absent 1/15.

Synovial TNCC was available for 13/21 elbows, with a mean of 102.2 +/- 55.8 x 10^9 cells/L (range of 13.7 – 183). The TNCC was below the inclusion level defined in this study for septic arthritis of 50 x 10^9/L in 2/13 (15.4%) cases (cases 14 and 21). In both these cases the

polymorphonuclear differential was greater than >90%. Case 14 was included due to resolution in clinical signs following antibiotic therapy and case 21 subsequently had a positive bacterial culture. Cytological assessment was available for 20/21 elbows. Based on the differential cell count, polymorphonuclear cells predominated in all cases (mean 91.4 +/- 5.1% of the TNCC population). Degenerate neutrophils were present in only one case (1/20) and intracellular bacteria were seen in five cases (3/5 subsequently having a positive culture result). Synovial fluid was submitted for culture in 21 cases with a positive culture obtained in 11/21 cases (52.3%). Bacteria cultured included *Staphylococcus aureus* (n=4), *Staphylococcus pseudintermedius* (n=3), *Streptococcus canis* (n=2), *Streptococcus agalactiae* (n=1) and a multi-organism culture (*E.coli, Enterococcus faecalis, Staphylococcus pseudintermedius*) (n=1). Antibiotic therapy had been given in 3/21 cases prior to referral and subsequent culture and sensitivity results; two of these (both post-TPLO infection), subsequently had a positive synovial fluid culture. Urinalysis was performed in 5/21 cases with a positive (*S. aureus* and *E. coli)* urine culture in two of these (Case 1 and 7). In Case 7, bacteria isolated from the bladder (*S. aureus*) matched the synovial fluid suggesting a haematogenous origin. Dogs were treated either medically with antibiotics only (n=16), or surgically by joint lavage and antibiotics (n=2, cases 5 and 7), or arthroscopy, joint lavage and antibiotics (n=3, cases 6, 9 and 10). Joint lavage involved placement of an ingress and egress needle and flushing of the joint with 1-2 litres of isotonic solution. The decision in treatment strategy was determined by the clinician at the time of diagnosis. In cases for which arthroscopy was performed (cases 6,9 and 10) arthroscopy, this was justified to manage concurrent medial compartment disease of the elbow. Antibiotic therapy included amoxicillin/clavulanic acid[f] (n=12), amoxicillin/clavulanic acid[f] and enrofloxacin[g] (n=6), cephalexin[h] and enrofloxacin[g] (n=1), cephalexin[h] (n=1). For all 11 elbows with a recorded antibiotic sensitivity, the instigated empirical antibiotic therapy was appropriate. Antibiotic therapy was continued for a mean of six weeks +/- 1.7 weeks.

Short-term follow-up information (<8 weeks) was available for 18/21 elbows. Of the dogs for which further information was not available, two were euthanatised whilst hospitalised due to deterioration in their condition and one was lost to follow-up. In all dogs that survived to discharge there was an improvement from pre-treatment lameness score [pre-treatment 7.5/10 (range 1-10) vs post-treatment 3/10 (range 1-5)] within the treatment period. Cases that had surgical management (n=5) had pre-treatment lameness of 7/10 (range 1 – 10) vs post-treatment 4.5/10 (range 1 – 5). Those that were managed medically had pre-treatment lameness of 9/10 (range 1-10) vs post-treatment 3/10 (range 2-5). Case 9 had an acute deterioration in lameness five days after cessation of a four week antibiotic course (amoxicillin/clavulanic acid) and a subsequent repeat culture and sensitivity revealed ongoing infection (*S. pseudintermedius*). This dog subsequently improved with additional antibiotic therapy (cephalexin[h]) for eight weeks but had residual lameness (1-2/10) at its last follow-up 12 months after diagnosis.

Medium to long-term follow (>8weeks) information was available for 12/21 cases (median 57 weeks; range: 14 weeks – 7 years). Recurrence of infection was recorded in 3/12 (25%) occurring at 14 weeks (Case 4), 1.2 years (Case 1) and 3.8 years (Case 6) after original diagnosis. Initial treatment in these three cases had included antibiotic therapy only in cases 1 and 4, and arthrotomy, joint lavage and antibiotic therapy in case 6. Residual lameness attributable to the elbow joint, based on owner follow-up was seen in 11/12 cases. The median lameness score was 3/10 (range 2 – 5). Case 8 had progressive ongoing lameness that was treated with total elbow replacement at another referral institution.

Discussion:

This is the first retrospective case series to focus solely on spontaneous septic arthritis of the canine elbow. It was the authors' experience that the elbow is one of the most common joints to spontaneously develop septic arthritis, when excluding surgical site associated infections (<1 month prior if no implants, <1 year if implants present) (10). A preliminary review of all cases of septic arthritis was performed during data collection for this manuscript. Fifty cases of spontaneous septic arthritis were identified during the study period and the elbow had the highest prevalence within this group (21/50, 42%). In a similar smaller retrospective series, when recent surgical cases were removed, the elbow was again the predominant joint, 8/14 cases (57%) (5).

In people, certain conditions are considered risk factors including rheumatoid arthritis or osteoarthritis, old-age, skin infection, cutaneous ulcers, diabetes, joint prosthesis, intra-articular corticosteroid injection and intravenous drug abuse (4, 15-17). These risk factors appear to be in accordance with our findings in dogs in that 85% of dogs were middle aged or older (mean age 6.8 years), and pre-existing osteoarthritis was present in 93% of cases in which imaging of the elbow was available, and concurrent medical conditions in 43% of our case population. Both ALL and anal furunculosis are treated with immunosuppressive therapy and it is likely the conditions and/or the treatment had contributed to the risk of septic arthritis developing in cases 6 and 14 (15). The presence of a transcondylar screw in case 17 potentially contributed to the development of infection. Surgical implants can act as a nidus for infection and subsequent removal of the implant and prolonged antibiotic therapy resulted in clinical improvement in case 17.

The main clinical signs seen in dogs with spontaneous septic arthritis of the elbow joint was joint effusion (100%), pain on joint manipulation (100%), and acute deterioration in lameness

(76%). Pyrexia was an inconsistent clinical finding (6/21- 29%), similar to a previous case series (19.4%) (5), although notably lower than post-surgical stifle sepsis (75%) (6). In this study, large breed dogs and breeds with a susceptibility to elbow dysplasia were most common (80%), likely reflecting a higher degree of underlying joint disease and osteoarthritis in these groups. In non-immunocompromised people, pre-existing joint disease is often identified, with osteoarthritis accounting for 33% of joint disorders (8, 17). Radiographic evaluation was available for 15 cases in the present series, and of these 14/15 (93%) had evidence of osteoarthritis. The high prevalence (11/15 cases, 73%) of severe radiographic OA, as found in our study, is in accordance with previous reports in which severe OA was present in 5/8 (62.5%) elbows (5).

A positive bacterial culture was obtained for 52% of cases, consistent with previous reports of variable positive culture rates (20-80%) (3,5,9,18). Interestingly, the use of antibiotic therapy prior to culture in three cases did not appear to affect outcome. In 2/3 cases given antibiotic therapy prior to sampling, two still had a positive culture. There is conflicting information in the literature regarding the influence of antibiotics on culture success. Pre-culture antibiotic therapy has been linked with false-negative results in several studies, whilst others have reported no difference in culture success (3,5,9). Despite this, current recommendations are to perform arthrocentesis prior to initiation of antibiotic therapy. In this study, *Staphylococcus spp.* were the most common bacteria isolated (63.6%) followed by *Streptococcus spp* (27%), which is similar to previous reports ranging from 42-59% (5-6) and 16-24% respectively (3). Two dogs had positive urine cultures, with one dog having similar bacteria isolated from both urine and synovial fluid. This finding highlights the importance of evaluating all potential sources of bacteria when a haematogenous origin is suspected. Importantly, 48% of elbows in the present study had a negative culture and relied on a presumptive diagnosis based on high

TNCC, predominance of polymorphonuclear cells and response to therapy. In two elbows the TNCC was below the cut-off value for septic arthritis (50 x 10^9 cells/L), however they were included in the study based on other criteria: a high percentage of neutrophils, response to antibiotic therapy and subsequent culture results in one elbow (11). The presence of a monoarthropathy with a predominantly neutrophilic cytology from synovial fluid sampling may be the only indication of septic arthritis/infection. This can make diagnosis and ruling out conditions like immune-mediated polyarthropathies challenging. To that end, other diagnostic tests have been sought, such as molecular methods (bacterial rRNA gene sequencing), analysis of synovial lactate concentration and use of leukocyte esterase and glucose reagent strips (18-21). However, even these new avenues for diagnosis are not without constraints, with comparisons between synovial fluid culture and rRNA PCR analysis not being able to demonstrate improved accuracy in diagnosis, and a wide reported 95% confidence interval in the sensitivity of lactate to predict septic arthritis (Sensitivity 1.00, 95% CI: 0.63-1.00) (18, 21). Currently, synovial fluid inoculation into blood culture media, synovial biopsy and cytology examination are recommended (22, 27, 29, 30).

The vast majority of septic elbows were treated by antibiotic therapy alone. The initial response to treatment was very good (94% resolution) and there was no difference in the response between cases treated with antibiotics alone compared to cases that had joint lavage and/or arthrotomy. This finding concurs with previous studies suggesting non-surgical management with antibiotic therapy alone (3,6,23) is sufficient due to the excellent blood supply to joints. Skeletally immature patients, which were not part of this cohort, may have different considertions due to the vulnerable nature of the open physes to pressure, and hence, we do not have the evidence here to conclude that surgical management may not be needed. However, this conclusion should be interpreted with caution due to low case numbers and potential for

clinical treatment selection bias. Failure of treatment in case 9 was likely due to insufficient antibiotic treatment duration (four weeks) or inappropriate initial antibiotic implementation. Selection of surgical management may also have been reserved for more severely affected cases increasingly the risk of recurrence. However the retrospective nature of this report does not allow further investigation of this potential bias. Subsequent extended treatment in case 9 with cephalexin resulted in clinical resolution and a significant improvement in lameness (20mg/kg orally twice daily for eight weeks). Long term follow up in 12 cases revealed a 25% recurrence of infection which is higher than that found in a previous smaller case series (5). The high rate of recurrence in the elbow contrasts to that reported for septic arthritis of other joints such as the hip joint (0%), stifle (7%), or hock (0%) (4,23). In this series, recurrence occurred 14 weeks (case 4), 1.2 years (case 1) and 3.8 years (case 6) after initial diagnosis. The long periods between remission and recurrence are less suggestive of recrudescence of incompletely resolved infection and more likely a result of renewed inoculation of a vulnerable and compromised joint. However, it does remain possible that recurrence of infection may be a result of quiescent bacteria remaining in the joint post-antibiotic treatment, or could represent haematogenous reseeding from the same or a new focus elsewhere in the body and an underlying predisposition to infection (24,28). Case 4 may represent a late relapse due to insufficient antibiotic therapy duration (6 weeks), or represent a recurrence of infection since deterioration in lameness occurred following a period of eight weeks of minimal reported lameness. Both cases 1 and 6 had predisposing factors for joint infection (diabetes mellitus and skin/urinary infection) and likely represent true recurrence in a predisposed joint. It is postulated that synovial vascular changes present in OA joints predisposes them to initial colonisation, and re-colonisation post-treatment (11,24,31). In rheumatoid patients and OA human patients, altered joint structure, including thinner vascular canals associated with increased subchondral plate thickness, increased osteochondral vascular density may

contribute to bacterial seeding and an increased risk of infection (31). Analysis of both the migratory and phagocytic function of polymorphoculear cells in the synovial fluid of humans with osteoarthritis has shown a decreased function compared to rheumatoid patients. The altered function and potential anomalous joint structure may help to explain a component of the increased susceptibility of osteoarthritic patients to joint infections (8,25,31), although we do not know if this is the case in the clinical canine patient.

A major limitation in this study is the retrospective design and reliance on assessing outcome from clinical records and low case numbers due to the relatively uncommon nature of this condition. The assessment of outcome is further compounded by the presence of pre-existing joint disease in the majority of dogs. Inclusion criteria were chosen to avoid the possible inclusion of non-infective cases based on previously described criteria (26). However, due to the low positivity from synovial culture, diagnosis of infection is often presumptive and may have resulted of inclusion of aseptic joints.

In conclusion, middle aged, large breed dogs, with pre-existing arthritis, that suffer an acute onset lameness, with elbow joint effusion and discomfort, even in the absence of pyrexia, should be considered for septic elbow arthritis. Antibiotic treatment is effective when prolonged treatment is instigated (6-8 weeks) appropriately however owners should be warned and veterinarians need to be aware of the potential for recurrence (3,5-6,24). Although there is evidence supporting a good early/short term response to medical therapy for septic arthritis, further evaluation of the long term outcome and recurrence rates for dogs treated medically or surgically is warranted. In addition, improving the ability to rapidly and accurately diagnose cases is critical to allow appropriate and early implementation of therapy to our patients.

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Appendix Legend:

Signalment, Presentation, Treatment and Outcome of 21 cases of spontaneous septic arthritis presented to the contributing institutes between March 2007 and June 2015

Superscript:

a. Doxorubicin, Pfizer Ltd, UK
b. Vincristine, Hospira UK Ltd, UK
c. Cyclophosphamide, Baxter Healthcare Ltd., UK
d. Prednidale, Dechra, UK
e. Atopica, Elanco, UK
f. Noroclav, Norbrook Laboratories Ltd., North Ireland
g. Baytril, Bayer plc, UK
h. Cephacare, Animalcare Ltd, UK