INTRODUCTION:
Antibiotics as prophylactic agents are routinely administered into the human intervertebral discs via intravenous injection in order to prevent disc infection [1]. Successful intervention however requires that the drug reaches adequate inhibitory concentration levels throughout the disc.

In this study and in continuation of our earlier works, the penetration time-history of antibiotic cephazolin into the human lumbar disc is modeled for 150 min post-intravenous injection, simulating reported measurements of cephazolin concentrations performed simultaneously in blood and in lumbar discs of patients prior to spinal fusion [1]. Using reported in vivo measured boundary sources, we aimed to compute antibiotic concentration levels throughout the disc at different post-injection periods and to assess the critical disc regions with below inhibitory concentrations. The effect of endplate calcification seen in ageing, scoliosis, and degenerate discs on the concentration levels is also investigated. It is hypothesized that the central region of the disc nucleus could experience concentration levels substantially below required therapeutic values especially as the endplates calcify.

METHODS:
A transient axisymmetric model of a human lumbar disc [2] is used to simulate the in vivo measurements of antibiotic cephazolin penetration in human lumbar discs at different times after initial intravenous administration [1]. The disc finite element (FE) model consists of 4 regions (Fig. 2, nucleus NP, inner/outer annuli IA/OA, and cartilage endplate CEP) with distinct properties. The FE model is made of 3360 bilinear quadrilateral elements. The accuracy of mesh refinement and time increment was initially verified. The blood-disc partition coefficient is taken as 0.37 at the NP and 0.41 at the OA boundary whereas the diffusivity varies from 1.0e-10 m²/s in CEP and OA to 1.1e-10 m²/s in IA and 1.2e-10 m²/s in NP [3]. The input source supply via blood stream at the CEP and OA boundaries are based on measured concentrations in serum of patients at 7-137 min intervals after intravenous administration of 1 g cephalosporin dose (data points in Fig. 1). Due to the absence of data, 3 different supply source curves are assumed for the initial 0-7 min post intravenous injection period with the maximum concentration either at 7 min, at 1 min or at 30 s (Fig. 1). They all follow an identical decay curve in the subsequent 7-150 min period (R²=0.99). Moreover, to study the effect of endplate blockage expected in degenerate discs, the concentration profile histories, the CEP diffusivity was reduced from the fully permeable condition (100%) to 50%, 25% or 10%. The transient diffusion model is solved with commercial program COMSOL.

RESULTS:
Computed cephazolin concentrations were in general agreement with reported measured values ranging from 0 to 9.5 mg/L in the disc tissue excised during surgery [1]. Changes in source supply curves in the initial 0-7 min period (Fig. 1) had negligible effects on concentrations at longer periods. Cephazolin concentrations in the disc were highest in the CEP (Fig. 2) where decay in concentrations (not shown) followed a similar time course to that in the blood (Fig. 1). By contrast in the IA and NP, concentrations increased with time after injection though to much lower levels that were practically non-detectable in the central region of the disc (Fig. 3). Endplate blockage markedly decreased cephazolin concentrations, especially in NP (Fig. 3). Taking 1 mg/L as the critical inhibitory concentration level [1], most of NP was deprived of cephalosporin at all times and for all CEP conditions (Figs. 2 and 4).

DISCUSSION:
Subject to reported measured in vivo concentration levels in blood stream following 1 g intravenous administration [1], the pharmacokinetics of the cephazolin transport in the human intervertebral disc was computed during 0-150 min post-injection period. Predicted concentrations were in overall agreement with those measured [1].

The post-injection variation of cephazolin concentration in the disc adjacent to source supply regions at OA and CEP closely followed the decay curve in the blood stream (Fig. 1) and sharply fell with time. A reverse trend was noted in remaining regions at IA and NP away from the blood source where the concentration levels actually increased with time up to 150 min (Fig. 3), a trend that most likely reverses had longer times been considered. The antibiotic level was, however, very low in the disc nucleus and remained for the most part below the 1 mg/L critical inhibitory concentration required to combat some bacterial infections [1] (Figs. 2 and 4). Considering that even greater critical values of about 8 mg/L is needed to prevent some other bacteria [1], the results of the current study clearly indicate that the disc nucleus region as well as a part of the neighboring IA remain at risk of bacterial infection. This situation deteriorates even further with lesser antibiotics reaching the central disc regions as the endplates calcify. With the gradual blockage of the endplate, the model predicted that nearly all the nucleus region was deprived of the minimum inhibitory antibiotic concentration of 1 mg/L. Such low antibiotic concentrations, even below the detectable levels, are also seen in in vivo studies [1].

Alterations in the endplate permeability have thus a profound effect on concentration profiles at all times and especially in the nucleus region (Figs. 3 and 4), demonstrating its crucial role on the delivery of nutrients, drugs, and injected solutes into the disc as confirmed earlier [2]. This highlights the crucial role of the degeneration state of the intervertebral disc in the success of drug/antibiotic delivery. Moreover, the predicted substantial drop in concentrations in the disc regions further away from the blood supply sources underlines the anticipated decrease in antibiotics concentration levels expected in larger lumbar discs. The foregoing concerns cast doubt and calls for caution in attempts to directly extrapolate findings of studies on animals with smaller and non degenerate discs to the human discs.

SIGNIFICANCE:
With current modes of administering intravenous antibiotics, the major portion of human lumbar discs experiences antibiotic concentration levels well below the required inhibitory levels against infection. Calcification of endplates lowers concentrations even further. ACKNOWLEDGEMENTS: Supported by the NSERC-Canada and the EU FP7 (grant agreement no. HEALTH-F2-2008-201626).

REFERENCES: