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Review

Review of Intra-Articular Use of Antibiotics and Antiseptic Irrigation and Their Systematic Association with Chondrolysis

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ABSTRACT

Introduction. Intra-articular antibiotics have been proposed as a treatment for septic arthritis to allow for high local concentrations without subjecting a patient to the toxicity/side effects of systemic therapy. However, there is concern for chondrotoxicity with intra-articular use of these solutions in high concentrations. The purpose of this systematic review was to evaluate the intra-articular use of antibiotics and antiseptic solutions, and to determine their association with chondrolysis following *in vitro* or *in vivo* administration.

Methods. A systematic review was conducted following PRISMA guidelines through PubMed, Clinical Key, OVID, and Google Scholar. Studies in English were included if they evaluated for chondrotoxicity following antibiotic exposure.

Results. The initial search resulted in 228 studies, with 36 studies meeting criteria. These 36 studies included manuscripts that studied 24 different agents. Overall, 7 of the 24 (29%) agents were non-chondrotoxic: minocycline, tetracycline, chloramphenicol, teicoplanin, pefloxacin, linezolid, polymyxin-bacitracin. Eight (33%) agents had inconsistent results: doxycycline, ceftriaxone, gentamicin, vancomycin, ciprofloxacin, ofloxacin, chlorhexidine, and povidone iodine. Chondrotoxicity was evident with 9 (38%) agents, all of which were also dose-dependent chondrotoxic based on reported estimated half maximal inhibitory concentrations (est. IC50): amikacin (est. IC50 = 0.31-2.74 mg/mL), neomycin (0.82), cefazolin (1.67-3.95), ceftazidime (3.16-3.59), ampicillin-sulbactam (8.64 - >25), penicillin (11.61), amoxicillin (14.01), imipenem (>25), and tobramycin (>25). Additionally, chondroprotective effects of doxycycline and minocycline were reported.

Conclusions. This systematic review identified agents that may be used in the treatment of septic arthritis. Nine agents should be avoided due to their dose-dependent chondrotoxic effects. Further studies are needed to clarify the safety of these medications for human intra-articular use. ***Kans J Med 2023;16:272-276***

INTRODUCTION

Septic arthritis (SA) is an orthopaedic emergency with the potential to impact both life and function.[1] Globally, there are approximately six to ten cases of SA per 100,000 people per year.[2] Even with prompt treatment, SA has a 90-day mortality rate of 7.05%, and in cases of those older than 79 years, the mortality rate increases three-fold. Following resolution of SA, patients develop accelerated secondary osteoarthritis at six times the rate seen in the general population.[3]

Irreversible cartilage damage in SA initially occurs via bacterial toxins and the host immune response.[4] Following a joint aspiration to confirm the diagnosis of SA[5], prompt arthroscopic or open irrigation and debridement is the first line of treatment.[6-8] Infection elimination can be challenging, as antibiotic courses are highly dependent on the agent's ability to penetrate the joint tissues.[9]

Intra-articular (IA) administration of antimicrobial agents allows for maintenance of high local concentrations above the minimum inhibitory concentration in the affected joint, without subjecting a patient to systemic toxicity and other serious side effects.[10,11] IA antibiotics during arthroscopic or open debridement in cases of SA is associated with decreased intravenous antibiotic use, a shorter period required for normalization of C-reactive protein-level, and fewer days admitted to the hospital.[11] In fact, antibiotics are the most common additive to irrigation solutions used in orthopedic procedures.[12] Additionally, prophylactic IA antibiotics commonly are used on grafts during ligament reconstruction.[13,14]

A concern with IA use of antibiotic and antiseptic solutions is that high concentrations may become chondrotoxic and cause further irreversible joint damage, worsening patient outcomes. The purpose of this study was to evaluate the IA use of antibiotics and antiseptic solutions, determine their association with chondrolysis following *in vitro* or *in vivo* administration, and identify the dosages at which they become chondrotoxic.

MATERIALS AND METHODS

Search Strategy and Study Selection. A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15] Institutional review board approval was not required, as all searches were completed on public databases. A systematic literature review was conducted in April 2022 using the PubMed, Clinical Key, OVID, and Google Scholar databases. A broad search was performed to identify studies that contained variations of the following terms: ("Chondrocytes" OR "Cartilage" OR "Chondrolysis" OR "Chondrotoxicity") AND ("Intra-articular antibiotics" OR "Intra-articular dilute chlorhexidine" OR "Anti-bacterial agents" OR "Povidone-iodine" OR "Iodopovidone" OR "Betadine" OR "Polyvidone iodine"). MeSH terms and a variety of word combinations were used. Duplicates were removed, and the remaining titles and abstracts were screened independently by two reviewers (H.P. and M.B.), who compared final results in order to minimize any possible bias. Included studies were those written in the English language that evaluated for chondrotoxicity following *in vitro* or *in vivo* intra-articular exposure to an antibiotic, chlorhexidine, or betadine. Exclusion criteria consisted of studies written in a non-English language, if the full text was not accessible via library, if the agent discussed is only approved

for use in animals, if the agent is not used to treat bacterial infections, if the agent was administered orally or intravenously, or if the study did not assess chondrotoxicity. A full-text review of the studies that met inclusion criteria was completed. References from each selected article were additionally screened.

Data Extraction. The following data were extracted and summarized: agent names, concentrations, half maximal inhibitory concentrations (IC50), type of animal or human model, and major conclusions. The primary outcome was any conclusion on chondrotoxicity and/or chondrocyte viability/cell death following exposure to the tested agent.

Data Synthesis. The concentrations were converted to mg/mL in order to easily compare studies that tested the same agent(s). Comprehensive tables were created and organized by drug name.

RESULTS

Search Results. The results of the comprehensive literature search are displayed in Figure 1. Overall, 228 studies were identified from the initial search. Following duplicate removal, 128 records remained, with 41 meeting criteria for full-text review. Once the full-text review was completed, 28 studies remained. The references of these included records were then screened for any additional eligible studies, and eight more studies were identified, which brought the total number of included studies to 36 (Table 1; Available online only at journals.ku.edu/kjm). In total, 24 agents were identified in the search. Many of the included manuscripts studied multiple agents, and some studies included both *in vivo* and *in vitro* portions of the study within a single manuscript. Therefore, all portions of these 36 manuscripts are listed separately by row in Table 1. Table 2 summarizes the seven agents which were found to be non-toxic, and the nine agents which were found to have dose-dependent toxicity.

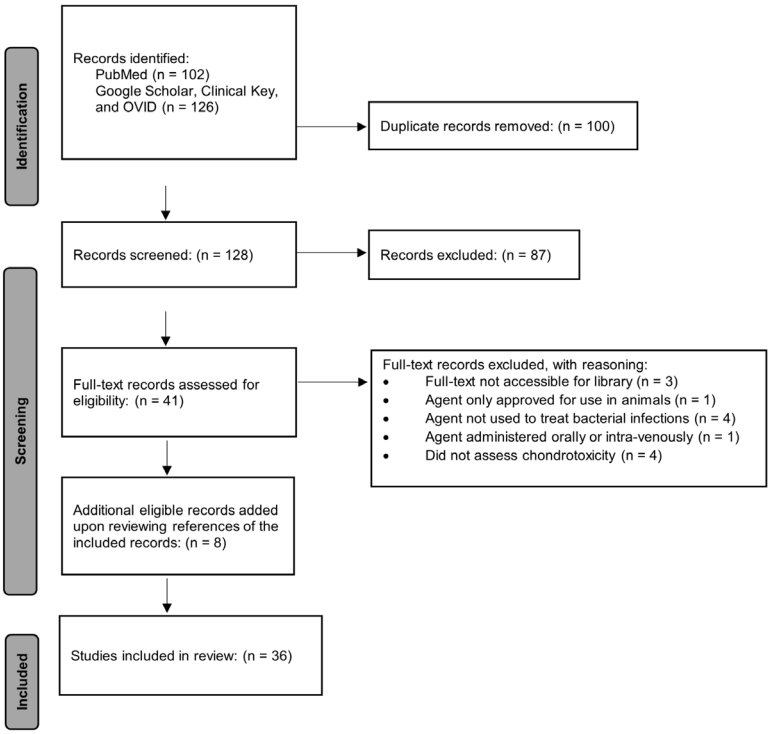

Figure 1. PRISMA Flow diagram for study selection.

Table 2. Summary of non-chondrotoxic vs. chondrotoxic agents.

Non-Chondrotoxic	Dose-Dependent Chondrotoxicity (est. IC50)
Minocycline	Amikacin (0.31-2.74 mg/mL)
Tetracycline	Neomycin (0.82 mg/mL)
Chloramphenicol	Cefazolin (1.67-3.95 mg/mL)
Teicoplanin	Ceftazidime (3.16-3.59 mg/mL)
Pefloxacin	Ampicillin-Sulbactam (8.64 - >25 mg/mL)
Linezolid	Penicillin G (11.61 mg/mL)
Polymyxin-bacitracin	Amoxicillin (14.01 mg/mL) Imipenem (>25 mg/mL) Tobramycin (>25 mg/mL)

Tetracyclines. Doxycycline has been noted to have a variety of effects on articular cartilage ranging from chondroprotective to chondrotoxic. Two out of eight studies (25%) that looked at doxycycline found it to be chondrotoxic.[19,20] Lu et al.[19] found that human chondrosarcoma cells treated with doxycycline at 50 µg/mL was cytotoxic. Similarly, Pezzanite et al.[20] found doxycycline to be chondrotoxic to *in vitro* equine cells with an IC50 of 1.031. Other studies did not demonstrate this same chondrotoxicity.[18,19] For instance, Yue et al.[23] found that doxycycline decreased chondrocyte apoptosis, increased type II collagen synthesis, and increased mechanical integrity. Doxycycline has also been shown to protect the articular environment through decreased expression of catabolic cytokines.[21,22]

Four studies included in this review assessed minocycline, another antibiotic from the tetracycline class. Unlike doxycycline, minocycline did not demonstrate the chondrotoxic side effects reported by Lu et al.[19] and Pezzanite et al.[20] for doxycycline. At dosages ranging from $5x10^{-5}$ to 0.046 mg/mL, no chondrotoxicity was noted, as determined via indicators of cell viability.[18,24] Studies by Fortier et al.[22] and Yamamoto et al.[25] found minocycline to have a chondroprotective effect by reducing articular cartilage damage following injury. Steinmeyer et al.[18] also found that tetracycline ranging from $4.0x10^{-4}$ to 0.044 mg/mL did not demonstrate chondrotoxicity in a bovine model.

Penicillins/Aminopenicillins. Three studies examined antibiotics in the penicillin and aminopenicillin class. Amoxicillin and ampicillin at dosages ranging from 0.39 – 25 mg/mL in equine and canine models demonstrated dose-dependent chondrotoxicity.[20,26] Ampicillin-sulbactam, alongside vancomycin, had the highest estimated IC50 as compared to the other antibiotics studied in canines.[26] Penicillin G, at dosages ranging from 0.39 – 100 mg/mL in bovine and equine models, also demonstrated dose-dependent chondrotoxicity, as indicated by diminished detection of mitochondrial dehydrogenases and less viable cells detected with trypan blue exclusion staining.[20,27]

Cephalosporins. From the four included studies on the cephalosporin class, cefazolin doses ranging from 0.39 to 50 mg/mL demonstrated dose-dependent chondrotoxicity.[20,26,28] Ceftazidime in doses ranging from 0.39 to 25 mg/mL also demonstrated dose-dependent chondrotoxicity.[20,26] Although Gunal et al.[29] did not find ceftriaxone to be chondrotoxic in a leporine model, they did not report a dosage used.

In addition, ceftriaxone at 4.17 – 50 mg/mL in a canine model did demonstrate dose-dependent chondrotoxicity.[28]

Aminoglycosides. Four out of the eight aminoglycoside studies assessed amikacin, which demonstrated dose-dependent chondrotoxicity in canine and equine models.[20,26,30,31] For gentamicin, three studies[32-34] did not demonstrate chondrotoxicity, while Pezzanite et al.[20] did find dose-dependent chondrotoxicity in an equine model. Pezzanite et al.[20] also looked at neomycin and tobramycin at 0.39 – 25 mg/mL in an equine model and found both exhibited dose-dependent chondrotoxicity, while Antoci et al.[35] found that tobramycin was chondrotoxic at all doses in a murine model.

Glycopeptides. Eight included studies evaluated glycopeptide antibiotics. Teicoplanin was not found to be chondrotoxic in a murine model,[36] and teicoplanin at 0.064 mg/mL in a human model also did not demonstrate chondrotoxicity.[37] The included studies on vancomycin found a variety of effects ranging from no chondrotoxicity to dose-dependent chondrotoxicity. Three vancomycin studies did not demonstrate chondrotoxicity,[34,36,37] while two other studies did.[20,26] Three additional studies found dose-dependent chondrotoxicity starting at 0.5, 5, and 6.125 mg/mL, respectively.[35,38,39]

Fluoroquinolones. Six studies evaluated antibiotics within the fluoroquinolone class. Ciprofloxacin did not demonstrate chondrotoxicity below 0.2 mg/mL in a variety of animal models.[35,40,41] The studies of IA use of ofloxacin ranging from 0 – 0.1 mg/mL in leporine and canine models showed chondrotoxic effects,[42-44] although Thuong-Guyot et al.[41] did not find IA ofloxacin 0.01mg/mL to be chondrotoxic in a leporine model. The same study also did not find pefloxacin 0.001 – 0.1 mg/mL to be chondrotoxic.[41]

Miscellaneous Antibiotics. Chloramphenicol 0.025 – 0.1 mg/mL was not found to be chondrotoxic when used intra-articularly in leporine and human models.[29,45] Linezolid 0.032 mg/mL did not demonstrate chondrotoxicity in a human model.[37] Additionally, Goswami et al.[34] did not find polymyxin and bacitracin to be chondrotoxic in a human model. One study looked at imipenem 0.39 – 25 mg/mL and found it exhibited dose-dependent chondrotoxicity in an equine model.[20]

Antiseptics. Anderson et al.[46] did not find 0.05% chlorhexidine to be chondrotoxic in a canine model; however, Goswami et al.[34] found 0.05% chlorhexidine to be chondrotoxic in an *in vitro* human model. For povidone-iodine, four studies did not find it to be chondrotoxic;[29,34,48,52] however, three studies found povidone-iodine to be associated with chondrotoxicity.[49-51] The study by Goswami et al.[34] was the one study that utilized a human model, and they did not find chondrotoxicity with 0.30% povidone-iodine.

DISCUSSION

Septic arthritis is an orthopaedic emergency that can have long-term implications.[1] In the treatment of septic arthritis, IA antibiotic administration allows for high local concentrations of the antimicrobial without subjecting the patient to systemic therapy and its side effects;[10,11] however, a concern with IA use of antibiotics and antiseptic solutions is that high concentrations may become chondrotoxic and cause further irreversible joint damage and worsen patient outcomes. The purpose of this study was to evaluate the intra-articular use of antibiotics and antiseptic solutions, determine their association with chondrolysis following *in vitro* or *in vivo* administration, and identify the dosages at which they become chondrotoxic. Our results identify several agents with associations with chondrotoxicity. These include amikacin, neomycin, cefazolin, ceftazidime, ampicillin-sulbactam, penicillin, amoxicillin, imipenem, and tobramycin. Multiple other agents were not associated with chondrotoxicity. These non-chondrotoxic agents include minocycline, tetracycline, chloramphenicol, teicoplanin, pefloxacin, linezolid, and polymyxin-bacitracin.

Of the reviewed antibiotics, the majority of the studies reporting on the tetracycline class, including doxycycline, minocycline, and tetracycline did not demonstrate chondrotoxic effects, with several studies demonstrating chondroprotective effects for doxycycline and minocycline.[21-23,25] Only two studies reported chondrotoxicity with this antibiotic class and both were with doxycycline.[19,20] Pezzanite et al.[20] reported dose-dependent chondrotoxicity of doxycycline in an equine model, and the study by Lu et al.[19] was conducted in a human chondrosarcoma cell model, which reported chondrotoxicity starting at 0.05 mg/mL. Six other studies on doxycycline, four studies on minocycline, and one study reporting on tetracycline did not demonstrate chondrotoxicity in a variety of models that included bovine, leporine, equine, and human.

Another antibiotic that did not demonstrate chondrotoxicity was chloramphenicol. At dosages of 0.025 – 0.1 mg/mL, chondrotoxicity was not reported in either the leporine or human models.[29,45] Chloramphenicol may be safe for intra-articular human use, although more studies supporting the findings of these three studies are needed.

A third antibiotic for which most of the studies did not report chondrotoxicity was gentamicin. Two studies in equine models with dosages ranging from 0.1156 to 100 mg/mL, and one study utilizing a human model with a dosage of 0.08 mg/mL, did not demonstrate chondrotoxicity.[32-34] However, one study did show chondrotoxicity in an equine model at a dosage ranging from 0.39 – 25 mg/mL.[20]

No toxicity was noted for glycopeptide antibiotic teicoplanin in two studies, including one human model at 0.064 mg/m.[36,37] No chondrotoxicity was noted for linezolid at 0.032 mg/mL in a human model and for polymyxin 0.05 mg/mL and bacitracin 1.3 mg/mL in a human model.[34,37]

While there is some variability in the reported effects of IA fluoroquinolone use, all studies found ciprofloxacin to be safe for IA use below 0.2 mg/mL in animal models, while ofloxacin was shown to be chondrotoxic in three of the four studies in animal models.[35,40-44] Pefloxacin did not demonstrate chondrotoxicity in a leporine model.[41] These findings should be corroborated in human models prior to a recommendation for human use.

An antibiotic with an ambiguous effect on chondrocytes was the glycopeptide vancomycin. Three of the included studies on vancomycin noted no chondrotoxicity, while five reported some level of dose-dependent chondrotoxicity.[20,26,34-39] In the three studies utilizing human models, no chondrotoxicity was shown in two studies, while the

third study demonstrated dose-dependent chondrotoxicity starting at 6.125 mg/mL. These data are relevant as current literature promotes the efficacy of prophylactic graft soakings in 1-5 mg/mL vancomycin solution.[53-56]

Unlike gentamicin, all studies on the aminoglycosides amikacin, neomycin, and tobramycin demonstrated chondrotoxicity that was largely dose-dependent.[20,26,30,31,35] This dose-dependent chondrotoxicity was also present for all studies on the cephalosporins cefazolin and ceftazidime and for one of two studies on the cephalosporin ceftriaxone.[20,26,28] Dose-dependent chondrotoxicity was also noted for ampicillin-sulbactam and penicillin G.[20,26,27] Based on these studies, the IA use of these antibiotics should be avoided, although studies in human models would be useful to validate these findings.

For the antiseptic chlorhexidine, two animal studies did not find it to be chondrotoxic, but the human study of 0.5% chlorhexidine did find it to be chondrotoxic.[29,34,46] For povidone-iodine, results were mixed with four studies reporting no chondrotoxicity, while three reported damage to articular cartilage in animal models.[29,34,48-52] Due to the variability of these findings, caution should be exercised in IA use of these antiseptics.

Limitations. There are several limitations to this study. First, most of these studies were performed in animal models or *in vitro* human models, which may limit the applicability of the study results to *in vivo* human use. Second, there is a wide variety of methodologies of the included studies and dosages of IA antibiotic use, which precluded any meta-analysis and may also limit the generalizability of the included studies. In addition, the IC50 was variable in the studied antibiotics and often not determined.

CONCLUSIONS

In conclusion, this systematic review identified antimicrobial and antiseptic agents that may be used in the treatment of septic arthritis. The following agents should be avoided due to their dose-dependent chondrotoxic effects: amikacin, neomycin, cefazolin, ceftazidime, ampicillin-sulbactam, penicillin, amoxicillin, imipenem, and tobramycin. Further studies, especially in human models, are needed to clarify the safety of these medications for human intra-articular use.

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