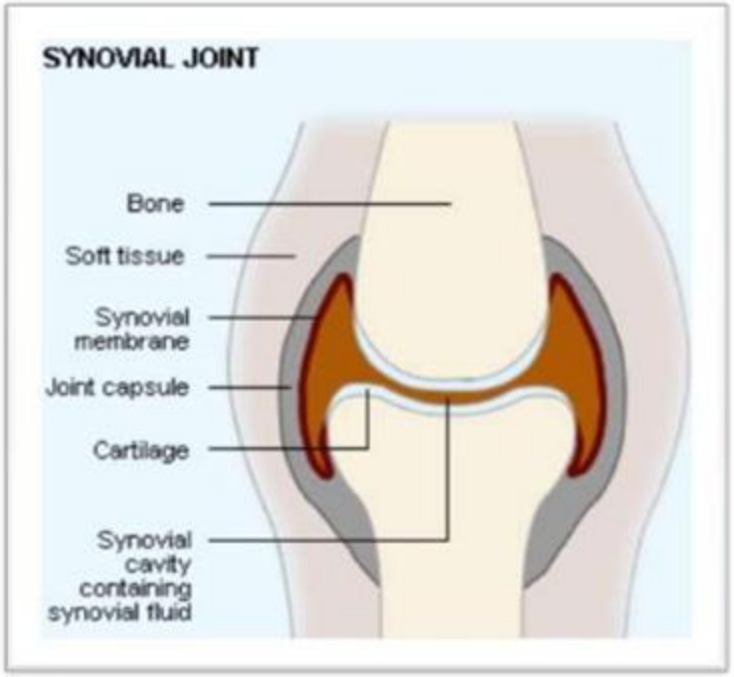
The beneficial effects of Corticosteroid for septic arthritis in children

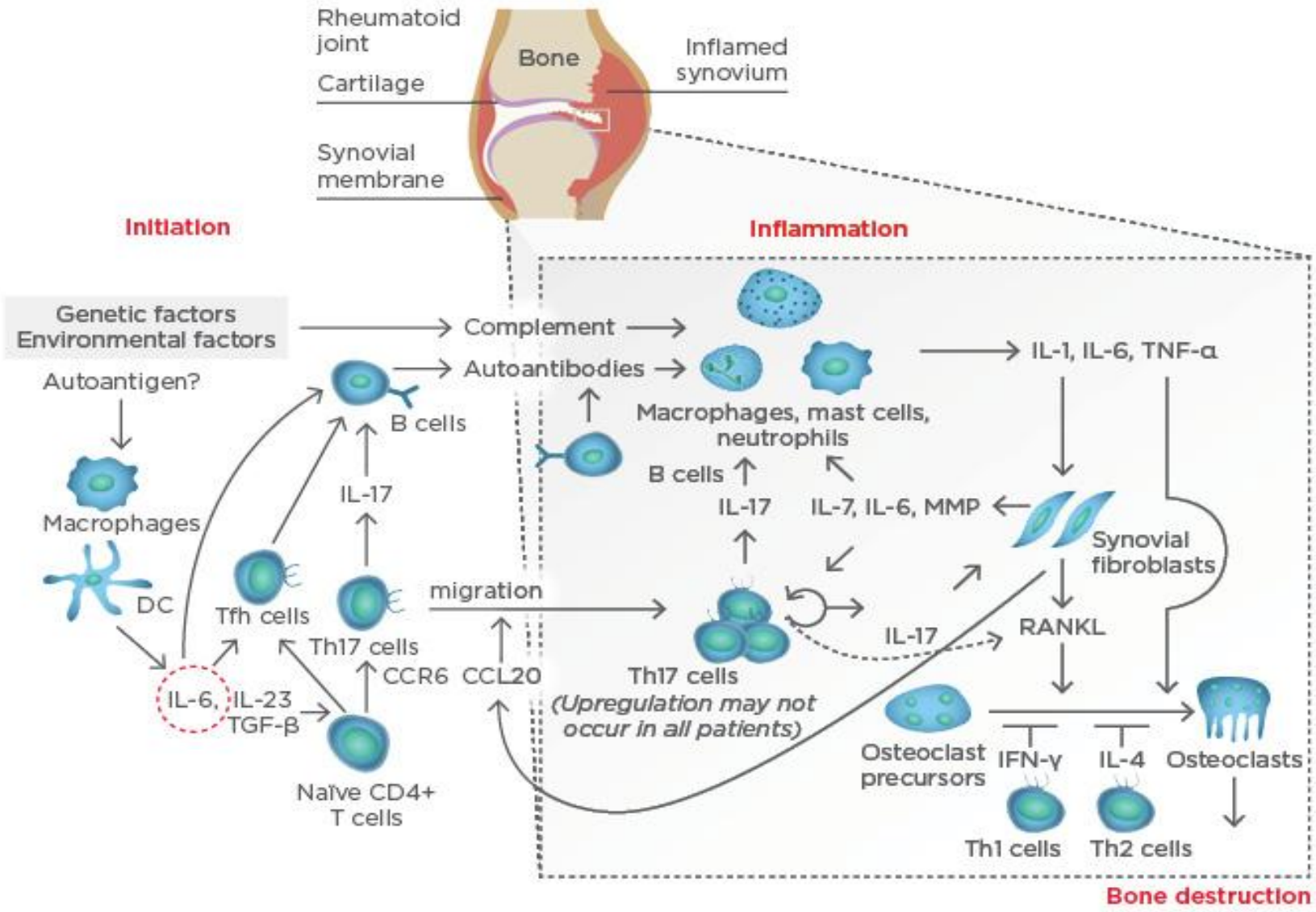
General pediatric Department

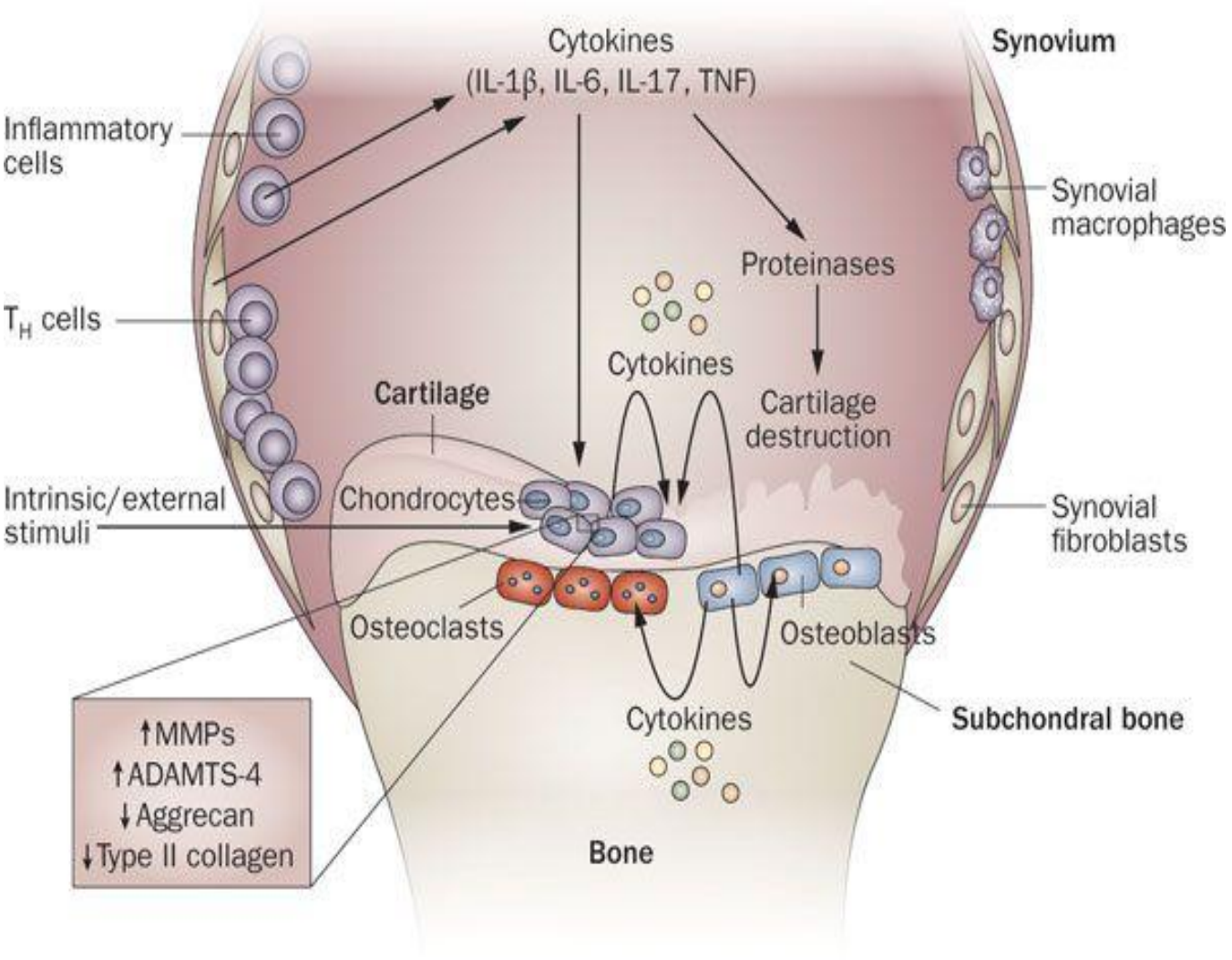
- **Septic arthritis** is inflammation of a synovial membrane with purulent effusion into the joint capsule, due to infection.

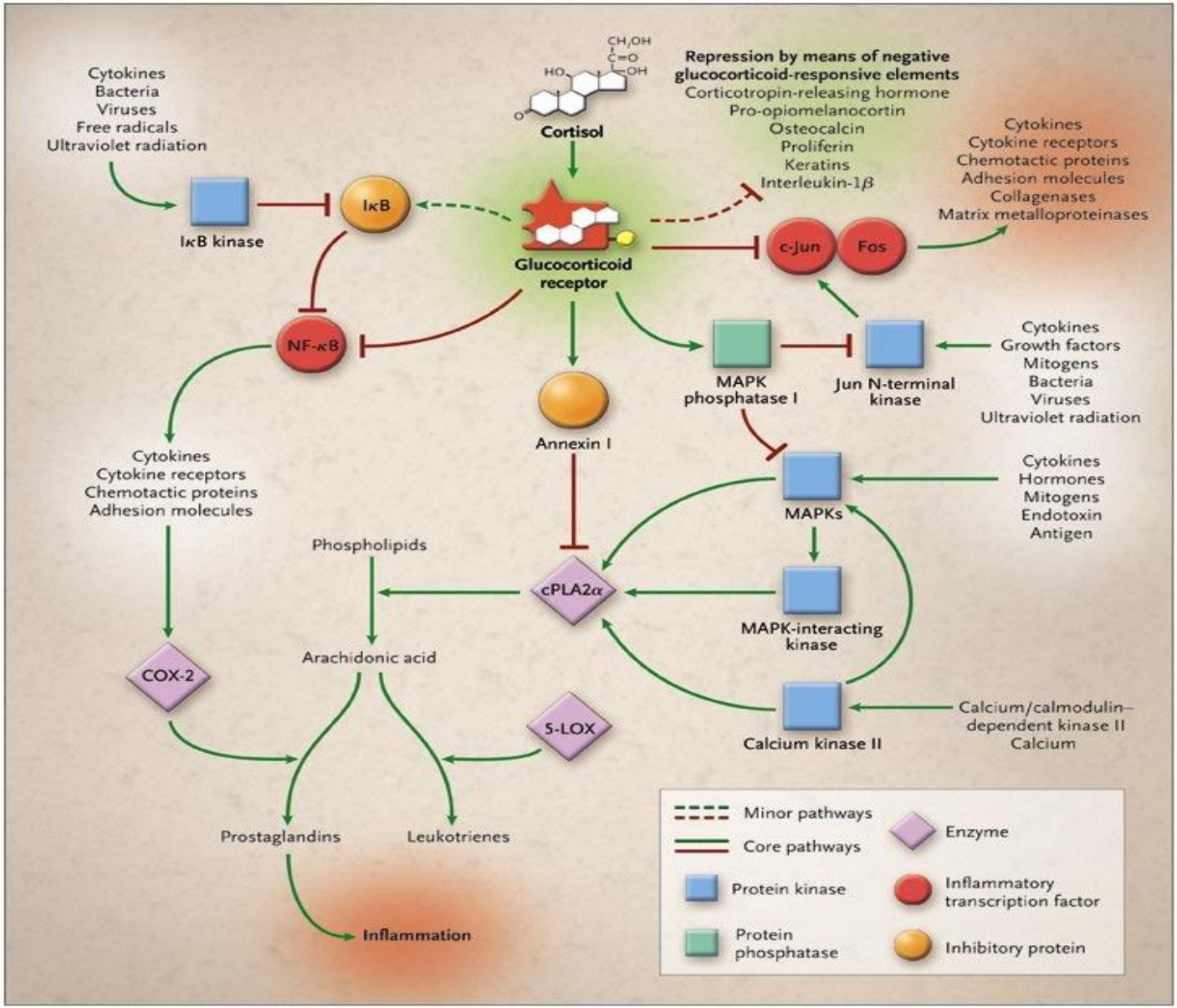


Synovial membrane

✓Membrane surrounding joint cavity
✓Produce synovial fluid
✓Contain rich capillary network for phagocytic and hyaluronate-producing function


Rheumatoid joint
Bone
Cartilage
Inflamed synovium
Synovial membrane
Initiation
Inflammation
Genetic factors
Environmental factors
Complement
Autoantibodies
IL-1, IL-6, TNF-α
Autoantigen?
B cells
Macrophages, mast cells, neutrophils
Macrophages
IL-17
B cells
IL-17
IL-7, IL-6, MMP
Synovial fibroblasts
DC
Tfh cells
Th17 cells
migration
IL-17
RANKL
IL-6, IL-23 TGF-β
CCR6
CCL20
Th17 cells
(Upregulation may not occur in all patients)
Osteoclast precursors
IFN-γ
IL-4
Osteoclasts
Naïve CD4+ T cells
Th1 cells
Th2 cells
Bone destruction


Cytokines
(IL-1β, IL-6, IL-17, TNF)
Synovium
Inflammatory cells
Synovial macrophages
Proteinases
T_H cells
Cytokines
Cartilage
Cartilage destruction
Intrinsic/external stimuli
Chondrocytes
Synovial fibroblasts
Osteoclasts
Osteoblasts
Cytokines
Subchondral bone
↑MMPs
↑ADAMTS-4
↓Aggrecan
↓Type II collagen
Bone


Cytokines
Bacteria
Viruses
Free radicals
Ultraviolet radiation
IκB kinase
IκB
NF-κB
Cortisol
Glucocorticoid receptor
Repression by means of negative glucocorticoid-responsive elements
Corticotropin-releasing hormone
Pro-opiomelanocortin
Osteocalcin
Proliferin
Keratins
Interleukin-1β
c-Jun
Fos
Cytokines
Cytokine receptors
Chemotactic proteins
Adhesion molecules
Collagenases
Matrix metalloproteinases
MAPK phosphatase I
Jun N-terminal kinase
Cytokines
Growth factors
Mitogens
Bacteria
Viruses
Ultraviolet radiation
Annexin I
Cytokines
Cytokine receptors
Chemotactic proteins
Adhesion molecules
MAPKs
Cytokines
Hormones
Mitogens
Endotoxin
Antigen
Phospholipids
cPLA2α
MAPK-interacting kinase
Arachidonic acid
COX-2
5-LOX
Calcium kinase II
Calcium/calmodulin–dependent kinase II
Calcium
Prostaglandins
Leukotrienes
Inflammation
Minor pathways
Core pathways
Protein kinase
Protein phosphatase
Enzyme
Inflammatory transcription factor
Inhibitory protein

Harel 2011

ORIGINAL ARTICLE

Dexamethasone Therapy for Septic Arthritis in Children

Results of a Randomized Double-blind Placebo-controlled Study

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Vered Hoffer, MD,†¶ Yosef Uziel, MD,†# and Jacob Amir, MD†‡

Background: We evaluated the effect of adding dexamethasone to antibiotic therapy in the clinical course of septic arthritis in children.

Methods: A randomized double-blind placebo-controlled trial was performed. The study group included 49 children with septic arthritis. In addition to antibiotic therapy given, patients were randomly assigned to receive intravenous dexamethasone 0.15 mg/kg every 6 hours for 4 days or placebo. The groups were compared for clinical and laboratory parameters, length of hospital stay, and late sequelae.

METHODS

A randomized double-blind placebo-controlled trial design was used. The study sample consisted of children aged 6 months to 18 years with septic arthritis who were hospitalized at Schneider Children's Medical Center of Israel and at Sapir Medical Center from March 1999 to December 2007. The diagnosis of septic arthritis was based on 3 criteria: (1) acute onset of swelling, pain, local warmth, and severe limitation of motion in any joint, except for the hip or shoulder, in which severe pain and limitation of motion were sufficient for diagnosis; (2) all involved joints were aspirated on admission. Joint fluid with a turbid purulent appearance and containing $\geq 50{,}000$ white blood cells (WBC)/mm^3 was considered septic; (3) elevated levels of acute phase reactants: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or WBC count. In all patients both synovial fluid and blood were cultured before treatment. The amount of joint fluid was assessed by ultrasonography in the hip and clinically in all other joints.

TABLE 3. Clinical and Laboratory Characteristics During Follow Up in Children With Septic Arthritis Treated With Antibiotics Plus Dexamethasone or Placebo

	1 (Dexamethasone) (n = 24) Mean (SD)	(Placebo) (n = 25) Mean (SD)	*P**
First day fever < 37°C	1.68 (2.57)	2.83 (2.41)	0.021
First day no local heat	5.50 (6.60)	7.31 (3.86)	0.028
First day no redness	1.18 (1.25)	3.38 (4.63)	0.172
First day pain free	7.18 (6.46)	10.76 (7.20)	0.021
First day full range of movement	7.00 (6.42)	12.24 (11.34)	0.030
First day normal function	6.64 (5.84)	8.71 (6.31)	0.102
Last day ESR > 25 mm/h	3.76 (4.50)	8.40 (7.14)	0.003
Last day WBC > 15,000/mm^3	2.65 (4.02)	1.32 (2.88)	0.186
Last day CRP > 0.5 mg/dL	3.09 (3.80)	5.48 (4.69)	0.029
Days IV	9.91 (4.84)	12.60 (5.20)	0.007
Days PO	14.67 (7.25)	14.41 (6.07)	0.986
Total days of antibiotic treatment	21.91 (8.57)	22.40 (8.00)	0.708

*Nonparametric Mann-Whitney nonparametric *U* test.

CRP indicates C-reactive protein; ESR, erythrocyte sedimentation rate; IV, intravenous; PO, per os; WBC, white blood cells

Outcome at Follow Up

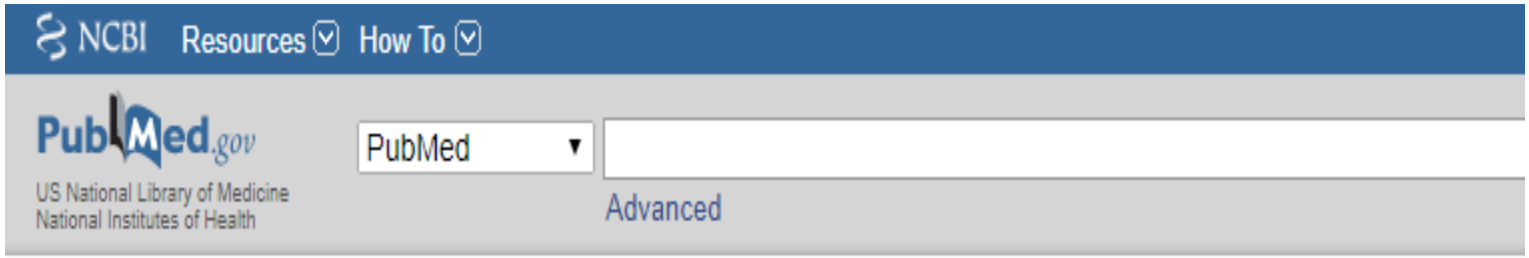
Long-term Outcome

After hospitalization, 45 of the 49 patients were followed for 2 months, 39 for 6 months, and 29 for 12 months (all patients were invited but only part of them showed up, probably because of lack of symptoms). Among these 29 children, 17 belonged to the dexamethasone group. None demonstrated adverse effects on outcome or functional sequelae of the involved joints. Range of motion of the involved joints was completely normal, symmetric to the noninvolved corresponding joints. No leg length discrepancy was noted. In the absence of symptoms or clinical findings, no radiographs were performed to reduce radiation. Additional follow up

Conclusions: A 4-day course of dexamethasone given at the start of antibiotic treatment in children with septic arthritis, is safe, and leads to a significantly more rapid clinical improvement, shortening duration of hospitalization compared with those treated with antibiotics alone.

Level of Evidence: I.

Fogel 2015



Format: Abstract

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Dexamethasone Therapy for Septic Arthritis in Children.

Fogel I[1], Amir J[2], Bar-On E[3], Harel L[4].

Author information

METHODS

Patients and Setting

A retrospective cohort study design was used. The sample consisted of children aged 2 months to 18 years hospitalized at our tertiary pediatric medical center from January 2008 (the end of our previous prospective study) to December 2013 who were discharged with a diagnosis of septic arthritis. Exclusion criteria were history of chronic arthritis, autoimmune disease, or immune deficiencies and arthritis secondary to a puncture wound. In addition, the medical records from discharge to last clinic follow-up visit were reviewed, and patients in whom another diagnosis was suspected on the basis of the follow-up data were excluded, as were patients with <6 months' follow-up.

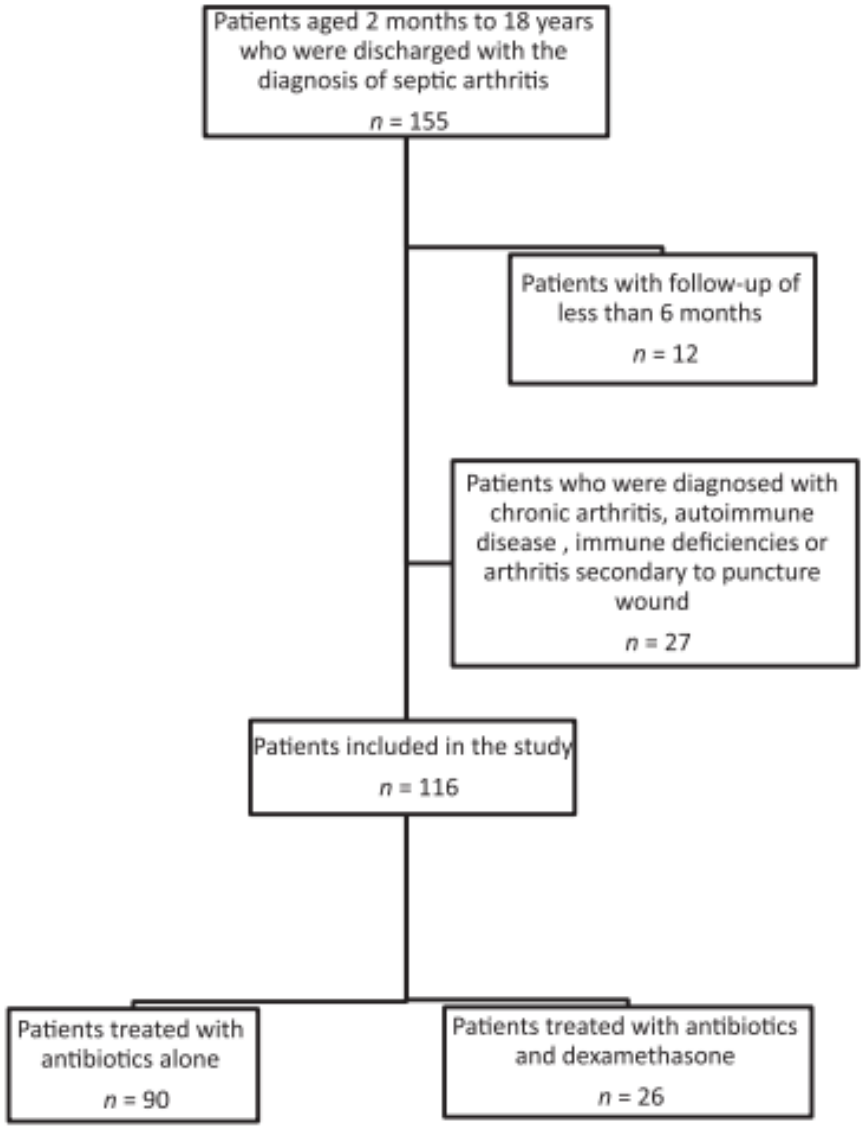


FIGURE 1
Flowchart of patient selection for the study.

In the present cohort, some of the patients were treated with antibiotics alone, whereas others were treated with intravenous dexamethasone 0.15 mg/kg per dose every 6 hours for 16 consecutive doses along with antibiotics, as previously reported. The administration of corticosteroids depended on the policy of the specific admitting department and was determined at the discretion of the attending physician. The switch from intravenous to oral treatment was based on a decrease in CRP to <1 mg/dL.

TABLE 4 Clinical and Laboratory Parameters of Improvement in Children With Septic Arthritis Treated With Antibiotics Alone or With Dexamethasone

Parameter	Antibiotics, Mean (95% CI)	Antibiotics and Dexamethasone, Mean (95% CI)	P^a
First day fever <38°C	3.9 (2.9–4.9)	2.3 (2.1–2.5)	.002
First day CRP <1 mg/dL	8.4 (6.9–9.9)	5.3 (4.0–6.6)	.002
Hospital stay, d	10.7 (9.4–12.1)	8.0 (6.8–9.2)	.004
Duration intravenous treatment, d	11.4 (9.7–13.1)	7.1 (5.9–8.3)	<.001
Time to full recovery, d	10.0 (8.5–11.6)	6.3 (4.9–7.7)	<.001

CI, confidence interval.

[a] Brown-Forsythe test (variances not assumed to be equal, following Levene test for variances).

- A short course of dexamethasonegiven early in addition to antibiotics to children with septic arthritis leads to significant clinical and laboratory improvement, shortens the duration of treatment, and accelerates recovery.
- Further studies are needed to examine possible long-term sequelae in children treated with antibiotics with or without adjunctive dexamethasone

Cochrane Library

Cochrane Database of Systematic Reviews

Corticosteroids for septic arthritis in children (Review)

Delgado-Noguera MF, Forero Delgadillo JM, Franco AA, Vazquez JC, Calvache JA

ABSTRACT

Background

Septic arthritis is an acute infection of the joints characterised by erosive disruption of the articular space. It is the most common non-degenerative articular disease in developing countries. The most vulnerable population for septic arthritis includes infants and preschoolers, especially boys. Septic arthritis disproportionately affects populations of low socioeconomic status. Systemic corticosteroids and antibiotic therapy may be beneficial for treatment of septic arthritis. Even if the joint infection is eradicated by antibiotic treatment, the inflammatory process may produce residual joint damage and sequelae.

Objectives

To determine the benefits and harms of corticosteroids as adjunctive therapy in children with a diagnosis of septic arthritis.

Search methods

We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library, Latin American Caribbean Health Sciences Literature (LILACS), the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/), ClinicalTrials.gov (www.ClinicalTrials.gov), and Google Scholar. We searched all databases from their inception to 17 April 2018, with no restrictions on language of publication.

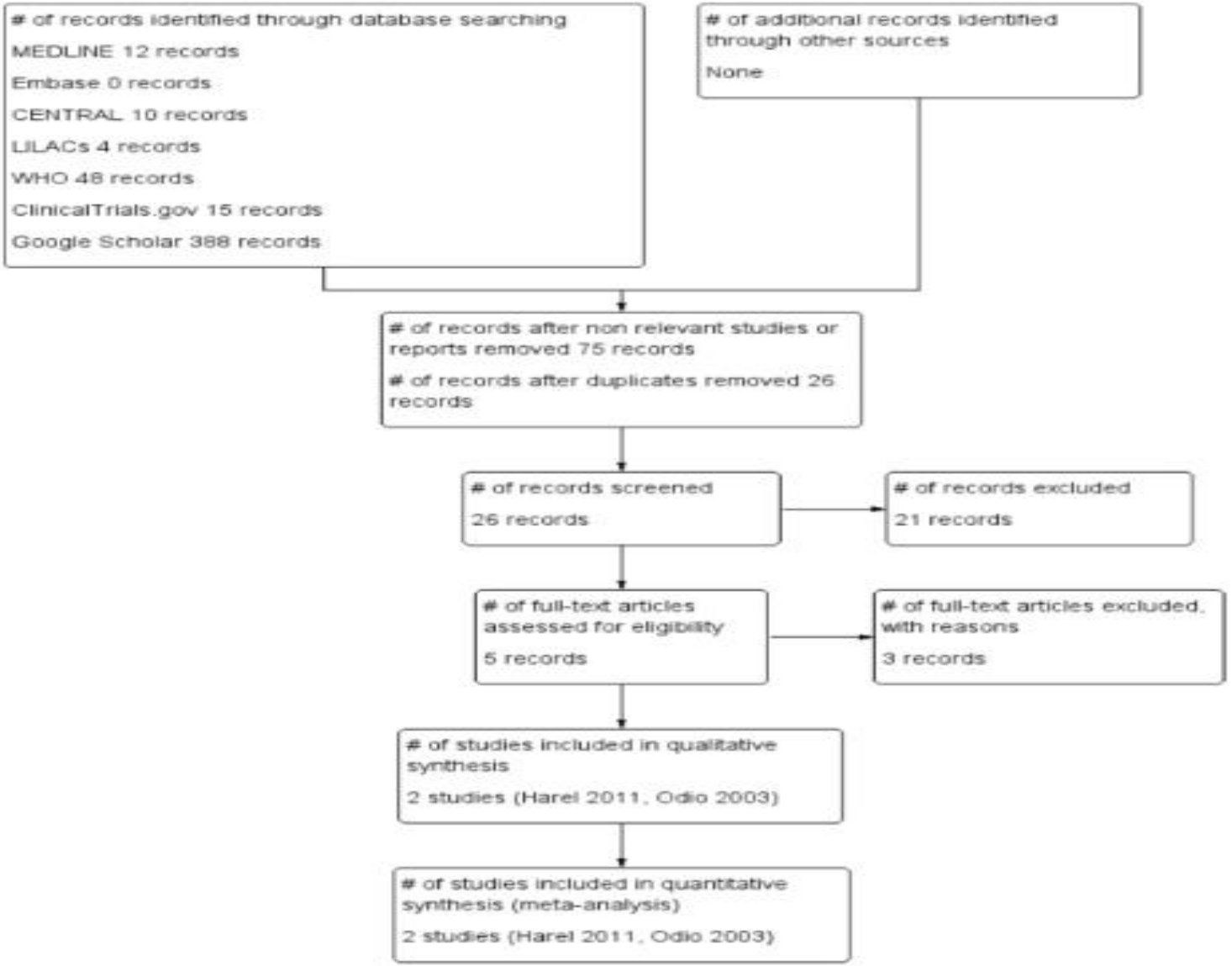
Selection criteria

We included randomised controlled trials (RCTs) with patients from two months to 18 years of age with a diagnosis of septic arthritis who were receiving corticosteroids in addition to antibiotic therapy or as an adjuvant to other therapies such as surgical drainage, intra-articular puncture, arthroscopic irrigation, or debridement.

Data collection and analysis

Two review authors independently assessed eligibility, data extraction, and evaluation of risk of bias. We considered as major outcomes the presence of pain, activities of daily living, normal physical joint function, days of antibiotic treatment, length of hospital stay, and numbers of total and serious adverse events. We used standard methodological procedures expected by Cochrane. We assessed the evidence using GRADE (Grading of Recommendations Assessment, Development and Evaluation) and created a 'Summary of findings' table.

Figure 1. Study flow diagram.



Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study Weaknesses
Odio C. and al 2003 Costa Rica	123 children from 3 months to 13 years old with suspected hematogenous bacterial arthritis received, with antibiotics, Dexamethasone 0,2mg/kg/dose q 8h or saline for 4 days. 100 were evaluable (50 in each group)	Double-blind randomized-control trial	Residual dysfunction of the articulation at the End of the therapy	4% (Dex) vs 32% (placebo) p = 0,00068	No primary outcome identified 23 patients not evaluated (5 met exclusion criteria and 18 were considered non bacterial synovitis) No mention of the side effects
			Residual dysfunction of the articulation at the 6 months	2% (Dex) vs 37% (placebo) p = 0,00007	
			Residual dysfunction of the articulation at the 12 months	2% (Dex) vs 26% (placebo) p = 0,00053	
			Time to resolution of symptoms	2.34 Â± 5.06 d (Dex) vs 7.81 Â± 2.04 d (placebo) p = 0,001	
Harel, L. and al 2011 Israel	49 children aged 6 months to 18 years with hematogenous bacterial arthritis received, with antibiotics, Dexamethasone 0,15mg/kg/dose q 6h (24 patients) or saline (25 patients) for 4 days.	Double-blind randomized-control trial	First day <37Â°C (primary outcome)	1.68 Â± 2.57 d (Dex) vs 2.83 Â± 2.41 d (placebo) p= 0.021	Multiple primary outcomes 20 patients lost to follow-up for late sequelae Small study No mention of the side effects
			First day pain free (primary outcome)	7.18 Â± 6.46 d (Dex) vs 10.76 Â± 7.20 d (placebo) p= 0.021	
			First day pain free (primary outcome)	7.00 Â± 6.42 d (Dex) vs 12.24 Â± 11.34 d (placebo) p=0.03	
			Presence of late sequelae (Secondary outcome)	None in the two groups	

For children with septic arthritis who are taking antibiotics compared to placebo (fake medicati

1. Corticosteroids may reduce pain in affected joints at one year of follow-up
2. Corticosteroids may improve normal function of affected joints at one year of follow-up
3. Corticosteroids may reduce days of intravenous antibiotic treatment needed
4. Corticosteroids may have little or no effect on total or serious adverse effects

We do not have information about the effects of corticosteroids on activities of daily living.

What happens to children with septic arthritis who take corticosteroids in addition to antibiotics?

Absence of pain

1. 24 more of 100 children experienced absence of pain after 12 months with corticosteroids (24% absolute improvement)

2. 96 of 100 children experienced absence of pain compared to 72 of 100 children who took a placebo

Activities of daily living

Included studies did not report this outcome.

Normal physical joint function

1. 24 more of 100 children who received corticosteroids had normal function of the joint after 12 months (24% absolute improvement)

2. 98 of 100 children experienced absence of pain compared to 74 of 100 children who received a placebo

Number of days of intravenous antibiotic treatment

1. Children who received corticosteroids compared with placebo had 2.77 fewer days of intravenous antibiotic treatment

2. Children who received corticosteroids had 8.09 days of intravenous antibiotic treatment

3. Children who received placebo had 10.86 days of intravenous antibiotic treatment

Length of hospital stay

1. We are uncertain whether corticosteroids had an effect on the length of hospital stay because the evidence was of very low quality

Total or serious adverse events

1. None of the patients treated with corticosteroids reported adverse effects at 12 months

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Corticosteroids compared to placebo for septic arthritis in children

Patient or population: septic arthritis in children taking antibiotics
Setting: hospitals in Costa Rica and Israel
Intervention: corticosteroids (dexamethasone)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with corticosteroids				
Pain - absence of pain at 12 months	72 per 100 (74 to 100)	96 per 100	RR 1.33 (1.03 to 1.72)	49 (1 RCT)	⊕⊕◯◯ LOW[a]	Absolute risk difference 24% (95% CI 5% to 43%) NNTB = 13 (95% CI 6 to 139)
Activities of daily living	See comments		-	(0 RCTs)	-	This outcome was not reported in any of the included trials
Number of participants with normal physical joint function - normal function at 12 months of follow-up (long term)	74 per 100 (83 to 100)	98 per 100	RR 1.32 (1.12 to 1.57)	100 (1 RCT)	⊕⊕◯◯ LOW[b]	Absolute risk difference 24% (95% CI 11% to 37%) NNTB = 13 (95% CI 7 to 33)
Number of days of antibiotic treatment - number of days of intravenous antibiotic treatment	Number of days of intravenous antibiotic treatment with placebo was 10.86	Number of days of intravenous antibiotic treatment with corticosteroids was 8.09	MD 2.77 lower (4.16 lower to 1.39 lower)	149 (2 RCTs)	⊕⊕◯◯ LOW[c]	Almost 3 days lower (95% CI 4 days to 1.5 days lower)

Length of hospital stay	See comments	-	(0 RCTs)	-	This outcome was not reported in any of the included trials. Study authors report that treatment with dexamethasone was associated with a shorter duration of IV antibiotic treatment, leading to a shorter hospital stay
Total adverse events at 12 months	See comments	-	49 (1 RCT)	⊕⊕◯◯ LOW[a]	Trial reported that none of the participants showed adverse effects
Serious adverse events at 12 months	See comments	-	49 (1 RCT)	⊕⊕◯◯ LOW[a]	Trial reported that none of the participants showed serious adverse effects

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; NNTB: number needed to treat for an additional beneficial outcome; RCT: randomised controlled trial; RR: risk ratio

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]We downgraded by one level for concerns about study limitations (high risk of attrition bias and selective reporting). We downgraded by another level for imprecision.
[b]We downgraded by one level for concerns about study limitations (unclear risk of detection and reporting bias and high risk of attrition bias). We downgraded by another level for imprecision.

Quality of the evidence

- Evidence for corticosteroids as adjunctive therapy in children with a diagnosis of septic arthritis is of low quality.

Conclusion

- Corticosteroids may increase the proportion of patients without pain and the proportion of patients with normal function of the affected joint at 12 months, and may also reduce the number of days of antibiotic treatment. However, we cannot draw strong conclusions based upon these trial results. Additional randomised clinical trials in children with relevant outcomes are needed


The End
Thank You!