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Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome secondary to antimicrobial therapy in pediatric bone and joint infections

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ABSTRACT

Background: Bone and joint infections are common in children, particularly those under 10 years of age. While antimicrobial therapy can often successfully treat these infections, surgical drainage may also be necessary. It is important to note that prolonged courses of treatment have been associated with adverse events and drug reactions. Among these, drug reactions with eosinophilia and systemic symptoms (DRESS) syndrome is particularly severe and potentially life-threatening. We aimed to evaluate the cases of DRESS syndrome that develop during the treatment of bone and joint infections.

Methods: A retrospective study was conducted at a tertiary-level university hospital between 2015 and 2022 to determine the incidence and outcomes of definite DRESS Syndrome in children under 18 years of age with bone and joint infections.

Results: Of 73 patients with bone and joint infections, 16 (21.9 %) children developed antimicrobial therapy-induced DRESS syndrome. Eight (50 %) of these children were boys; the mean age of the patients was 9.76 ± 5.5 years. DRESS syndrome occurred in 16 children, including 13 children with osteomyelitis, 1 child with osteomyelitis and septic arthritis, and 2 children with septic arthritis and sacroiliitis. The mean duration of intravenous antibiotic therapy was 40.6 ± 16.6 days; the mean hospital stay was 48.7 ± 23.7 days; the mean time for the development of DRESS syndrome after starting antibiotics was 19.6 ± 7.68 days. New onset fever (68.8 %) and rash (43.8 %) were the most common symptoms of DRESS Syndrome. Cefotaxime and vancomycin were drugs responsible for DRESS syndrome in 8 (50 %) of 16. The causative antibiotics were switched to another class of antibiotic, most commonly preferred was ciprofloxacin (n:5; 31.3 %). For children with persistent symptoms, steroids were used in 5 (31.25) patients.

Conclusions: Clinicians should be aware of DRESS syndrome in children who develop fever and rash under long-term antibiotics and should check hematological and biochemical parameters to

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predict the severity of DRESS syndrome. In patients with persistent symptoms, steroids may be used to control the symptoms.

Keywords: Bone and joint infection, DRESS syndrome, Children

INTRODUCTION

Bone and joint infections are serious infectious diseases which cause significant morbidity.[1] In the past, bone and joint infections were devastating and caused high mortality rates and complications.[1] Fortunately, the use of antibiotics and surgical treatment have significantly reduced the occurrence of complications associated with these infections. However, prolonged use of antibiotics may result in drug reactions, 1 of which is drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, a rare and unpredictable, life-threatening disease triggered by drugs that can cause long-lasting skin eruption and a mortality rate of approximately 10 %.[2] Classic symptoms of DRESS syndrome include a diffuse maculopapular rash, lymphadenopathy, visceral organ involvement such as liver, kidney, heart, lungs, endocrine system, facial edema, fever, and hematologic abnormalities such as eosinophilia, lymphocytosis, and atypical lymphocytes.[3] Although the incidence of DRESS syndrome in children is unknown, it appears to be lower than in adults.[4] The pathogenesis of DRESS syndrome is not yet fully understood, but it is thought to be related to drug hypersensitivity and underlying viral infection that leads to immunosuppression.[5–7] Anticonvulsants, antimicrobials, antivirals, antipyretic/anti-inflammatory analgesics, and antidepressants are among the drugs associated with DRESS syndrome.[8] Therefore, careful monitoring is crucial when using antibiotics, and prompt recognition and management of drug reactions are essential to minimize the risk of their complications.

It is known that the most common drugs causing DRESS syndrome are antibiotics and antiepileptics. Long-term use of drugs can cause DRESS syndrome. DRESS syndrome was not uncommon in our hospital in bone and joint infections requiring long-term antibiotic therapy. Therefore, in this study, DRESS syndrome is secondary to antibiotic treatment in children with bone and joint infections, and its treatment was evaluated in different aspects. As far as we know, this is the first comprehensive study to evaluate the prevalence, risk factors, and prognosis of DRESS syndrome in children with bone and joint infections.

STUDY DESIGN AND STUDY POPULATION

A single-center retrospective study was conducted at a tertiary university hospital in Turkey between 2015 and 2022. We included patients under 18 years of age who required hospitalization and intravenous (IV) therapy for suspected/confirmed osteomyelitis, septic arthritis, and spondylodiscitis. Osteomyelitis was diagnosed based on the presence of clinical features such as fever, pain, and restriction of movement in addition to histopathologic findings of inflammation in a surgical specimen of bone or detection of a pathogen through culture or Gram stain in an aspirate or biopsy of bone or the periosteal fluid collection or evidence of osteomyelitis in magnetic resonance imaging (MRI).[9] Septic arthritis was defined as the presence of clinical findings of joint infection such as wound discharge, redness, warmth, pain, and joint effusion demonstrated by ultrasound or by physical examination, and positive microbiological culture or Gram-strained smear.[10] Spondylodiscitis was diagnosed based on clinical and laboratory findings (elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)), or evidence of spondylodiscitis in MRI, and microbiological documentation from the spinal puncture or blood cultures.[11]

DRESS syndrome occurred in 16 (21.9 %) patients associated with used antibiotic treatment for bone and joint infections. The diagnosis of DRESS syndrome is primarily based on clinical features (cutaneous findings, systemic symptoms), history of exposure to drugs and high-risk drugs in the

previous two to eight weeks, and laboratory and imaging findings. We used the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring system to confirm or exclude the diagnosis of DRESS syndrome. We included only patients with RegiSCAR score ≥4.[4] Mild DRESS syndrome was defined as a condition in patients without clinical, laboratory, or imaging evidence of renal or pulmonary involvement and only showed a modest elevation of liver transaminases (Table 1).[12] On the other hand, severe DRESS syndrome was defined as cases in which patients exhibited severe, life-threatening organ involvement resulting in admission to the pediatric intensive care unit (PICU) or even death.[13] RegiSCAR scores were calculated according to the RegiSCAR score system.[14,15] In patients with RegiSCAR scores ≥4, we paused beta-lactam antibiotics, switched to another class of antibiotics, and checked the hemogram, all biochemical parameters, and viral serological assays. We also obtained all cultures to exclude nosocomial infections. We accepted a patient with DRESS syndrome after ruling out viral infections and nosocomial infections and according to diagnostic criteria. Therefore, patients with a viral infection and patients who developed DRESS due to other than bone and joint infections were excluded. We performed antinuclear antibodies, peripheral smear, serology for cytomegalovirus, herpesviruses, Epstein-Barr virus, hepatitis A/B/C, parvovirus B19, quantitative PCR for adenoviruses, influenza, coronavirus, rhinovirus, human herpesvirus 6, and Human herpesvirus 7 with DRESS children.

Children with severe underlying illnesses such as metabolic disorders, cardiopulmonary diseases, liver diseases, endocrinological and neuromuscular disorders, bone diseases, and immune deficiencies, as well as newborns under one month of age) and those with RegiSCAR score of less than four were excluded. Complications were defined as any clinical condition that developed after admission to the hospital, such as pyomyositis, abscesses, hospital-acquired infections, or deep venous thrombosis.

The first outpatient check-up of the children with DRESS was 15 days after discharge. Patients are still followed every 3–6 months. Patients with DRESS were followed for at least 1 year.

All children with bone and joint infections whose data could be accessed and those parents' accepted to be involved in the study were included in our study. SYA and ZSB collected the data.

DATA COLLECTION

Demographic and clinical data, including duration of symptoms, localization of arthritis, and

Mild DRESS syndrome	No/minimal visceral involvement (not reaching moderate DRESS syndrome thresholds)
Moderate DRESS syndrome	At least one visceral involvement of moderate severity: hepatic: ALT (4–15 N) and/or ALP (3–5 N); renal: organic kidney failure with increased creatinine of >26.4 mmol/L or 1.5 × N or oliguria <0.5 mL/kg/h; hematological: Hb (7–10 g/dL) and/or PNL (500–1500/mm^3) and/or platelets (50.000–100.000/mm^3) Absence of potentially life-threatening visceral impairment: heart, lung, neurological or digestive
Severe DRESS syndrome	At least one serious visceral problem: liver: ALT >15 N and/or ALP >5 N, factor V < 50 %; kidney: rapidly progressive organic kidney failure or oligo-anuria; interstitial pneumopathy with PaO_2 < 60 mmHg; myocarditis; neurological damage; digestive involvement; signs of hemophagocytosis

Table 1. Criteria used to assess DRESS syndrome severity on admission to our department. *ALT: alanine transaminase, ALP: alchalen phosphatase, hb: hemoglobin, PNL: polymorphonuclear lymphocyte, N: normal*

presence of fever, were collected for all patients. Laboratory data including complete blood count (CBC) (white blood cell [WBC], absolute neutrophil count [ANC], absolute lymphocyte count [ALC], hemoglobin [Hb], platelet count [PLT], eosinophil), CRP, pro-calcitonin (pct), ESR, urea, creatinine, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), albumin and the results of bacterial blood, punction, synovial cultures were also recorded at the beginning of hospitalization. CBC was performed on the Sysmex XN-3100™ Automated Hematology System (Sysmex). CRP was measured immunoturbidimetrically (CRPL4, Tina-quant CRP IV) in human serum on Cobas c systems (Roche Diagnostics GmbH) (Roche, Cobas®). All chemistry parameters were measured on Roche Cobas® 8000 modular analyzers (Roche Diagnostics).

Synovial fluid was evaluated for white blood cell counts, and microbiological examination results were recorded, including direct microscopic examinations and bacterial culture are performed. The management of arthritis was also evaluated, including the length of hospital stays, the administration, and the duration of antibiotic treatment and surgical interventions.

STATISTICAL ANALYSIS

Statistical analysis was performed using the SPSS statistical package (version 25 for Windows). Data were expressed as means ± SD or medians (interquartile range) for continuous variables or percentages for categorical variables, depending on the normality distribution. Clinical characteristics and laboratory variables were compared using the student *t*-test, the Mann–Whitney *U* test, the chi-square test, and Fisher's exact test. Spearman's test was used to evaluate correlations between variables. Statistical significance of differences and correlations were defined as a *p*-value of <0.05.

RESULTS

The study included 73 patients with confirmed cases of osteomyelitis, septic arthritis, and spondylodiscitis. Of these, 50 (68.5 %) had osteomyelitis, 9 (12.3 %) osteomyelitis and septic arthritis, 8 (11 %) septic arthritis, 3 (4.1 %) synovitis, 2 (2.7 %) septic arthritis and sacroiliitis, and 1 (1.4 %) spondylodiscitis. The mean age of the patient was 9.27 ± 5.67 years, and 38 (52.1 %) of patients were male. Fever was present in 16 (21.9 %) patients, and the most common locations of infection were the metatarsi (17.8 %), femur (15.1 %), and tibia (12.3 %). There were no significant differences in inflammatory parameters such as pct, WBC, or ESR between osteomyelitis and septic arthritis except for CRP value. CRP was higher in the septic arthritis group than in osteomyelitis (26.6 ± 44.9 vs 81.8 ± 66.8, $p = 0.04$). Among the 39 children with isolated microorganisms, methicillin-sensitive *S. aureus* was the most common (n:17, 23.3 %), followed by methicillin resistance *S. aureus* (n:5, 6.8 %), *Pseudomonas aeruginosa* (n:3, 4.1 %), *Streptococcus agalactia* (n:2, 2.7 %). Mortality was not observed. Initially, 70 (95.9 %) children received IV antibiotics, primarily vancomycin and cefotaxime (n:31, 42.5 %), followed by ampicillin-sulbactam (n:10, 13.7 %). The total treatment duration for osteomyelitis was 32.5 ± 16.3 days, while for septic arthritis, it was 25.1 ± 12.5 days. Surgery was performed on 30 (60 %) children with osteomyelitis, 7 (87.5 %) with septic arthritis, and 8 (88.9 %) with osteomyelitis and septic arthritis.

Sixteen children were confirmed to have DRESS syndrome, with 13 having osteomyelitis, 1 having osteomyelitis and septic arthritis, and 2 having septic arthritis and sacroiliitis. The mean age of these patients was 9.76 ± 5.5 years, and 8 (50 %) of them were male. The average time between the initiation of antibiotic treatment and the diagnosis of DRESS syndrome was 19.6 ± 7.68 days. Using severity criteria, 16 patients (100 %) were assessed as having mild/moderate DRESS syndrome, and none were classified as having severe DRESS syndrome. Eleven children (68.8 %) had a fever, 7 (43.8 %) had a rash, 15 (93.8 %) had eosinophilia, 13 (81.3 %) had higher CRP, 12 (75 %) had liver involvement, and 12 (75 %) had neutropenia. Fig. 1 shows mucocutaneous involvement in some patients. We did not determine any patient with pulmonary or renal involvement and face edema. Cefotaxime and vancomycin (n:8, 50 %) were the most frequently used antibiotics, followed by ampicillin-sulbactam (n:3; 18.8 %) and cefotaxime (n:2, 12.5 %). A pathogen was isolated in 8/16 patients. In 8 cases, a microorganism was isolated from the tissue culture, and in 2 cases, it was isolated from the puncture culture. Methicillin-sensitive *S. aureus* was

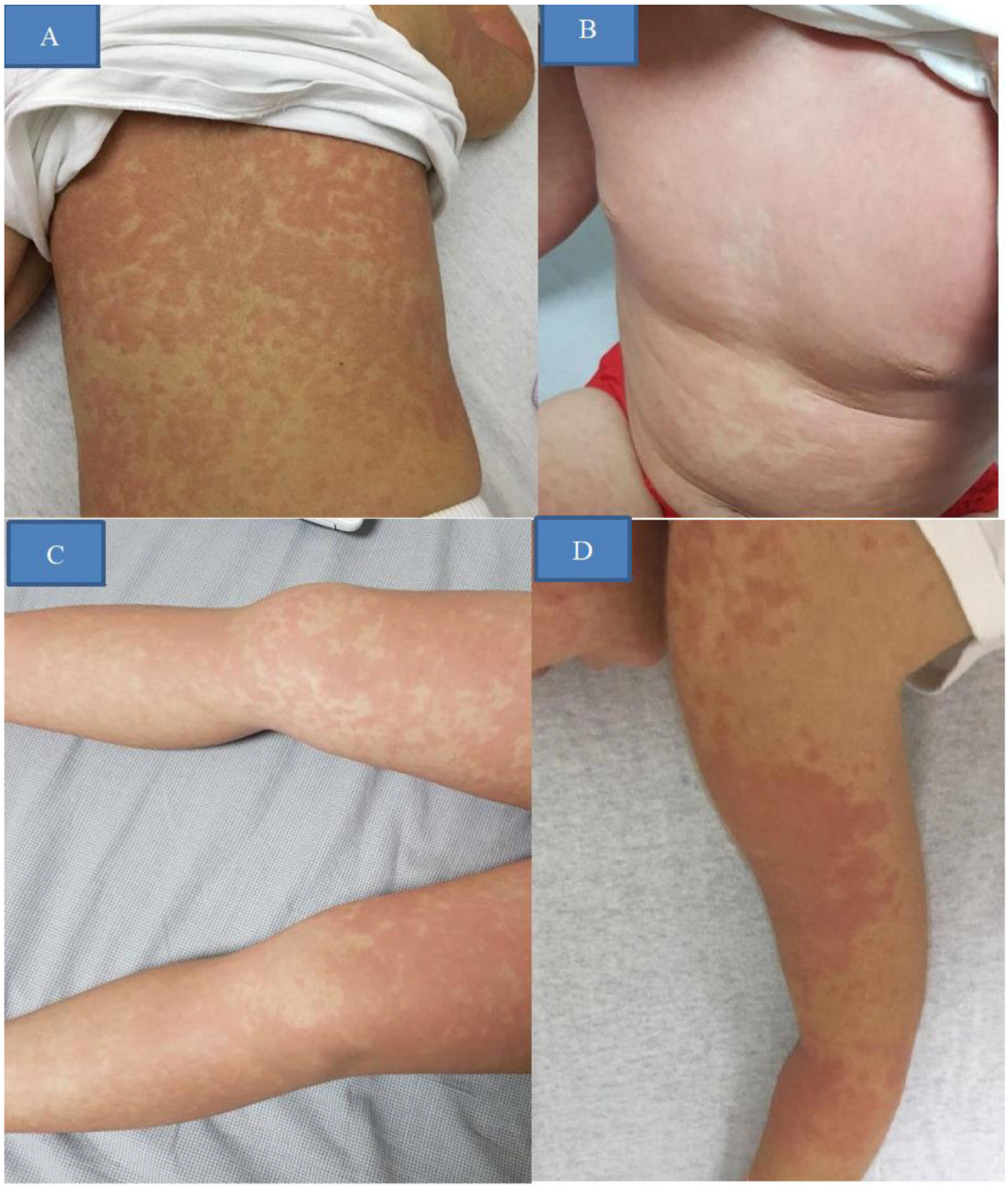

Fig. 1 Mucocutaneous involvement in some patients

the most common microorganism isolated. Table 2 summarizes the results of the children with DRESS syndrome. The mean duration of IV antibiotic therapy was 40.6 ± 16.6 days, and the mean length of hospitalization was 48.7 ± 23.7 days. Antibiotics were discontinued and switched to mostly ciprofloxacin (n:5, 31.3 %), or ampicillin-sulbactam (n: 2, 12.5 %), piperacillin-tazobactam (n:2,12.5 %). Antihistaminic treatment was required for 4 patients. Five (31.25 %) patients were treated with systemic glucocorticoids. None of the patients received intravenous immunoglobulin. DRESS syndrome resolved in an average of 10.06 ± 5.79 days. All patients recovered completely without any sequelae.

When comparing patients with DRESS syndrome and non-DRESS syndrome, there were no significant differences in terms of age and gender. The average length of hospitalization and duration of IV antibiotic therapy were significantly higher in the DRESS group than in the non-DRESS

	Patients with DRESS in bone and joint infections n:16	Patients with DRESS in other infections n:11	p-value (Odds ratio (95 % confidence interval))
Age, years (mean ± SD)	9.76 ± 5.5	5.95 ± 4.9	0.071
Sex, male (n,%)	8 (50)	9 (81.8)	0.093
Diagnosis of bone and joint infections (n,%)			
Osteomyelitis	13 (81.3)	-	-
Osteomyelitis and septic arthritis	1 (6.3)	-	-
Septic arthritis and sacroiliitis	2 (12.5)	-	-
Soft tissue infection	-	3 (27.3)	-
Deep neck infection	-	1 (9.1)	-
Orbital cellulitis	-	1 (9.1)	-
Central nervous system infection	-	3 (27.3)	-
Urinary tract infection	-	1 (9.1)	-
Mastoiditis	-	2 (18.2)	-
Associated very probable drugs (n,%)			
Vancomycin and cefotaxime	8 (50)	6 (54.5)	-
Ampicillin-sulbactam	3 (18.8)	-	-
Cefotaxime	2 (12.5)	1 (9.1)	-
Cefotaxime and teicoplanin	1 (6.3)	-	-
Vancomycin and meropenem	1 (6.3)	-	-
Cefazoline and rifampicin	1 (6.3)	-	-
Cefotaxime and clindamycin	-	2 (18.2)	-
Ampicillin-sulbactam and clindamycin	-	1 (9.1)	-
Teicoplanin	-	1 (9.1)	-
Time from antibiotic therapy to the onset of DRESS diagnosis (mean ± SD)	19.6 ± 7.68	16.9 ± 8.9	0.443
Severity of DRESS (n,%)			
Mild/moderate DRESS	16 (100)	11 (100)	-
Severe DRESS	0 (0)	0 (0)	-
Clinical presentation and laboratory findings (n,%)			
Fever	11 (68.8)	9 (81.8)	0.446
Rash	7 (43.8)	9 (81.8)	**0.048 (5.786 (0.935-35.814))**
Face edema	0 (0)	0 (0)	-
Eosinophilia	15 (93.8)	11 (100)	0.398
Higher CRP	13 (81.3)	9 (81.8)	0.970
Neutropenia	12 (75)	6 (54.5)	0.135
Leukopenia	11 (68.8)	4 (36.4)	0.096
Lymphopenia	9 (56.3)	4 (36.4)	0.310
Thrombocytopenia	2 (12.5)	1 (9.1)	0.782
Liver involvement	12 (75)	5 (45.5)	0.381
Pulmonary involvement	0 (0)	0 (0)	-
Renal involvement	0 (0)	1 (9.1)	0.219

(continued)

	Patients with DRESS in bone and joint infections n:16	Patients with DRESS in other infections n:11	p-value (Odds ratio (95 % confidence interval))
Positivity of culture (n,%)	8 (50)	6 (54.5)	0.816
Tissue culture (n,%)	8 (50)	2 (18.2)	0.093
Punction culture (n,%)	2 (12.5)	0 (0)	–
Isolated pathogens (n,%)			
Methicillin-sensitive *S. aureus*	1 (6.3)	0 (0)	–
Pseudomonas aeruginosa	1 (6.3)	0 (0)	–
Streptococcus agalactiae	2 (12.5)	0 (0)	–
Stenotrophomonas maltophilia	1 (6.3)	0 (0)	–
Streptococcus pyogenes	0 (0)	1 (9.1)	–
Methicillin-resistance *S. aureus*	0 (0)	1 (9.1)	–
Streptococcus pneumoniae	0 (0)	2 (18.1)	–
Escherichia coli	0 (0)	1 (9.1)	–
Escherichia coli and Streptococcus agalactiae	0 (0)	1 (9.1)	–
Duration of IV antibiotic therapy, day (mean ± SD)	40.6 ± 16.6	29 ± 14	**0.050**
Length of hospitalization day (mean ± SD)	48.7 ± 23.7	31.9 ± 15.8	**0.017**
Switched therapy (n,%)			
Ciprofloxacin	5 (31.3)	1 (9.1)	–
Ampicillin-sulbactam	2 (12.5)	2 (18.2)	–
Piperacillin-tazobactam	2 (12.5)	0 (0)	–
Meropenem	0 (0)	3 (27.3)	–
Clindamycin	1 (6.3)	2 (18.2)	–
Antihistaminic treatment (n,%)	4 (25)	11 (100)	**<0.001 (3.75 (1.620–8.679))**
Systemic glucocorticoids (n,%)	5 (31.25)	5 (45.5)	0.453

Table 2. (Continued) Demographics and characteristics of children with DRESS. *SD, Standard deviation; IV, intravenous; DRESS, Drug reaction with eosinophilia and systemic symptoms*

(29.8 ± 18 vs 48.7 ± 23.7, p = 0.007; 29.5 ± 16.3 vs 40.6 ± 16.6, p = 0.018). Laboratory values were similar in the 2 groups, except mean platelet volume (MPV) and pct. MPV was higher in the DRESS than the non-DRESS group (8.6 ± 1.9 vs. 10.1 ± 1.14, p < 0.001). Pro-calcitonin was lower in the DRESS group than in the non-DRESS group (p = 0.033) (Table 3). RegiSCAR score was positively correlated with lymphopenia (r = 0.525, p = 0.037). There was no relationship between eosinophils and disease score, length of hospital stays, and duration of treatment.

In our hospital, between 2015 and 2022, DRESS was detected in 11 patients with other than bone and joint infections. We observed that DRESS developed in 3 (1.3 %) of 225 children with soft tissue infection, 1 (2.3 %) of 43 children with deep neck infection, 1 (5%) of 17 children with orbital cellulitis, 3 (1.7 %) of 168 children with central nervous system infection, 1 (1.1 %) of 90 children with urinary tract infection, 2 (6.2 %) of 32 children with mastoiditis. When we compared patients with DRESS in other infections and bone and joint infections, there were no statistically significant differences in age, gender, or time from antibiotic therapy to the onset of DRESS diagnosis (p > 0.05) (Table 2). When evaluating the children with DRESS, the rash was a more common symptom in other infections than bone and joint infections

	DRESS N:16	Non-DRESS N:57	p-value	Odds ratio (95 % confidence interval)
Age, years (mean ± SD)	9.76 ± 5.5	9.14 ± 5.72	0.699	
Sex, male (n,%)	8 (50)	30 (52.6)	0.852	
Diagnosis of bone and joint infections (n,%)				
Osteomyelitis	13 (81.3)	37 (64.9)	0.214	
Osteomyelitis and septic arthritis	1 (6.3)	8 (14)	0.673	
Associated very probable drugs (n,%)				
Vancomycin and cefotaxime	8 (50)	23 (40.4)	0.490	
Ampicillin-sulbactam	3 (18.8)	7 (12.3)	0.681	
Cefotaxime	2 (12.5)	4 (7)	0.606	
Cefotaxime and teicoplanin	1 (6.3)	0 (0)	NA	
Vancomycin and meropenem	1 (6.3)	0 (0)	NA	
Cefazoline and rifampicin	1 (6.3)	0 (0)	NA	
Physical examination (n,%)				
Pain	10 (62.5)	35 (61.4)	0.936	
Fever	2 (12.5)	14 (24.6)	0.496	
Reduced range of motion	9 (56.3)	35 (61.4)	0.710	
Swelling	6 (37.5)	35 (61.4)	0.089	
Tenderness	8 (50)	25 (43.9)	0.663	
Warmth	2 (12.5)	13 (22.8)	0.367	
Location of bone-joint infections (n,%)				
Metatarsal	3 (18.8)	10 (17.8)	1	
Femur	3 (18.8)	8 (14)	0.697	
Tibia	2 (12.5)	7 (12.3)	1	
Positivity of culture (n,%)	8 (50)	31 (54.4)	0.756	
Tissue culture (n,%)	8 (50)	13 (22.8)	0.058	
Punction culture (n,%)	2 (12.5)	16 (28.1)	0.326	
Isolated pathogens (n,%)				
Methicillin-sensitive *S. aureus*	1 (6.3)	16 (28.1)	NA	
Pseudomonas aeruginosa	1 (6.3)	2 (3.5)	NA	
Streptococcus agalactia	2 (12.5)	0 (0)	NA	
Stenotrophomonas maltophilia	1 (6.3)	0 (0)	NA	
Duration of IV antibiotic therapy, day (mean ± SD)	40.6 ± 16.6	29.5 ± 16.3	**0.018**	
Length of hospitalization day (mean ± SD)	48.7 ± 23.7	29.8 ± 18	**0.007**	
Laboratory values (mean ± SD)				
WBC/mm^3	10,254 ± 4694	14,412 ± 29,866	0.582	
ANC/mm^3	6006 ± 3954	6570 ± 3803	0.605	
ALC/mm^3	3213 ± 2543	3221 ± 2139	0.991	
Hb (gr/dL)	11.3 ± 1.5	11.1 ± 1.8	0.692	
Plt/mm^3	372 ± 85.5	391 ± 139.5	0.589	
MPV (fL)	10.1 ± 1.14	8.6 ± 1.9	**<0.001**	
CRP (mg/L)	42.7 ± 63.7	40.6 ± 54.6	0.896	

(continued)

	DRESS N:16	Non-DRESS N:57	p-value	Odds ratio (95 % confidence interval)
Pct (µg/L)	0.07 ± 0.06	0.19 ± 0.28	**0.033**	
ESR (mm/h)	53.6 ± 37.5	49.8 ± 37.6	0.730	
AST (U/L)	37.6 ± 58.6	25.8 ± 10.9	0.434	
ALT (U/L)	37.4 ± 78.3	21.9 ± 22.3	0.448	
Albumin (mg/dL)	4.1 ± 0.47	3.96 ± 0.6	0.422	
Urea (mg/dL)	19.5 ± 6.2	19.1 ± 7.11	0.841	
Creatinine (mg/dL)	0.47 ± 0.16	0.40 ± 0.16	0.200	

Table 3. Comparison of clinical and demographical characteristics of DRESS and non-DRESS children. *ALC, absolute lymphocyte count; ANC, absolute neutrophil count; AST, aspartate transaminase, ALT, alanine transaminase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; MPV, mean platelet volume; Pct, procalcitonin; Plt, platelet count; WBC, white blood cell*

(p = 0.048), the duration of IV antibiotic therapy and length of hospitalization day were longer in bone and joint infection (p = 0.05, p = 0.017) (Table 2).

DISCUSSION

Bone and joint infections are common in the pediatric population. In recent years, morbidity and mortality rates have decreased due to improvements in diagnosis, surgical treatment, and antibiotic therapy. The treatment of bone and joint infections is at least four weeks. Antibiotic treatment is crucial in bone and joint infections; however, antibiotics can have some side effects and adverse drug reactions. DRESS syndrome is one of the drug reactions that can occur during prolonged antibiotic treatments in bone and joint infections. We determined DRESS syndrome in 21.9 % of our patients under antibiotic bone and joint infection treatment. In patients with DRESS syndrome, erythema on joints was more common, and the length of hospital stay and the duration of antibiotics were longer than in non-DRESS syndrome.

DRESS syndrome was initially described as associated with aromatic antiepileptic drugs, but later, it was understood that 50 different drugs, including allopurinol, trimethoprim-sulfamethoxazole, minocycline, vancomycin, sulfonamides can cause DRESS syndrome.[16] The incidence of DRESS can range from 0.01 to 0.7 cases per 1000 hospitalized patients, depending on the healthcare system and demographic context. In a recently published case series, it has been suggested that 15–37 % of DRESS syndrome may be caused by antibiotics.[17] A health record review in the United States from 1980 to 2016 showed that DRESS syndrome was due to antibiotics in 74 % of cases (vancomycin [39 %], β-lactams [23 %], fluoroquinolones [4 %], tetracyclines [4 %] and sulfonamides [3 %]).[18] In the review in 2021, 22 (8.6 %) of 254 cases were associated with penicillins, 17 of these 22 cases were from co-amoxiclav and piperacillin-tazobactam, 10 (3.94 %) were from cephalosporins, 8 of which were from third-generation cephalosporins, only 3 (1.18 %) were cases of carbapenem-induced DRESS, 46 (18.1%) were cases of vancomycin-associated DRESS.[19] In 2019, 15 of 1253 adult patients with tuberculosis receiving antituberculosis drugs were identified as potential cases of DRESS syndrome, and the prevalence of DRESS was 1.2 %.[20] The prevalence of DRESS in pediatric patients with bone and joint infections and DRESS in pediatric patients with other types of infections is still unknown, and there is no data in the literature. To date, only 3 cases of cefotaxime-induced and a few cases of vancomycin-induced DRESS syndrome have been reported in the literature.[21-26] Although cefotaxime is a safe drug and rarely associated with mild adverse reactions, in our study, we found that it was the most commonly used drug in children who developed DRESS syndrome. In certain studies, the diagnosis of DRESS syndrome was confirmed by patch testing, which could not performed in our study. We established the diagnosis of DRESS syndrome with clinical symptoms, laboratory features, and RegiSCAR scores. In our study, cefotaxime and vancomycin were responsible for 50 %, ampicillin/sulbactam for 18.8 %, and single cefotaxime 12.5 % for DRESS cases. In DRESS cases, the patch test

is useful in searching for the culprit is, and if negative, intradermal tests can be used. Another test is the lymphocyte transformation test, which can be useful in identifying the culprit drug by measuring lymphocyte proliferation in response to the drug in question.[27]

The underlying mechanism of DRESS syndrome has not been clarified. It has been suggested to be multifactorial, an immune-mediated hypersensitivity component that results from direct interaction between the drugs or their metabolites and genetic susceptibility.[28] Symptoms typically appear 2–8 weeks after the initiation of the triggering drugs.[29] In a prospective study, children receiving antibiotics developed DRESS syndrome an average of 5.8 days after treatment beginning.[30] Bedouelle et al[31] reported that the onset of DRESS syndrome occurred within an average of 6 (0–28) days. In our study, the mean duration between the initiation of antibiotics and DRESS syndrome was longer when compared to the aforementioned study. However, it should be noted that in the classical definition of DRESS syndrome, symptoms can develop 2–6 weeks after the initiation of treatment.[32]

DRESS syndrome is characterized by fever, rash, lymphadenopathy, elevated liver enzyme levels, and leukocytosis with eosinophilia. High fever usually begins at the reaction's start and always precedes the eruption.[33] Kardaun et al[4] reported that liver involvement was frequent (75 %), often manifesting as transient abnormality in liver function tests, involvement of the kidneys (37 %), and lung (32 %). Similar to previous studies, 11 (68.8 %) patients developed fever, 7 (43.8 %) developed rash, and 12 (75 %) had liver involvement. None of the patients had evidence of kidney or lung involvement in our study group.

In our study, we found that hematological abnormalities were prevalent and more diverse than previously reported in DRESS syndrome. This highlights the importance of conducting a complete blood count when diagnosing this condition. A previous study by Kardaun et al[4] reported that leukocytosis (95 %), transient eosinophilia (95 %), neutrophilia (78 %), and monocytosis (69 %) were common in DRESS syndrome. However, our study showed that transient eosinophilia was prevalent in 93.8 %, while leukopenia and neutropenia were seen in 68.8 % and 75 % of cases, respectively. In a case report, leukopenia was detected in a patient with DRESS 15 days after oral maxillofacial surgery and on installing the clinical DRESS syndrome.[34] Leukopenia began 1 month after the introduction of carbamazepine for partial epilepsy in an eight-year-old child, and there was leukopenia on the same day as the DRESS clinical symptoms in a report.[35] Another case report showed that the period between the onset of DRESS and the detection of agranulocytosis was 2–18 days.[36] Although leukocytosis is more commonly associated with DRESS syndrome, leukopenia may be observed in the initial period. We consider that the high incidence of leukopenia in our study can be attributed to the fact that patients had blood counts in the early phase of DRESS syndrome.

It is important to note that assessing the severity of DRESS syndrome remains a challenge.[16] In a case report, it was observed that eosinophil counts were positively correlated with the severity of DRESS symptoms, including skin rash and organ damage.[37] Eosinophilia could be a valuable indicator of disease progression and treatment response in DRESS patients.[37] However, in our study, no relationship was found between eosinophil count and disease score, hospital stay, and treatment duration. Instead, we found a positive correlation between the RegiSCAR score and lymphopenia.

Current treatment recommendations are based on case reports and expert opinion because there are no prospective clinical trials for the treatment of DRESS syndrome. The prompt cessation of the causative drug has a key role in treating DRESS syndrome.[38] Treatment is mainly supportive and symptomatic in mild forms, such as topical steroids and systemic anti-H1 antihistamines. In the severe form, the expert opinion of the French Dermatology Society recommends the administration of corticosteroids.[39] In 1 study, treatment consisted of topical corticosteroids in only 30.6 % and systemic corticosteroids in 55.1 %.[31] Systemic corticosteroids have been administered in 43–100 % of cases in both adults and children in several observational studies and literature reviews,[16,40,41] whereas the use of topical steroids is rarely reported.[40,41] We did not use topical steroids in our patients. In our study, 31.3 % of the

patients were treated with corticosteroids. Steroid treatment was initiated in patients with persistent rash and fever despite the antibiotic switch, while we did not observe exacerbation after tapering the steroid in our study.

Symptoms may persist for weeks or months, even if the causative drug is withdrawal.[42] We demonstrated that the DRESS syndrome resolved after an average of 10.06 ± 5.79 days. However, the hospital stay of our patients was significantly longer in our study. In the study by Bedouelle et al,[31] the average length of hospital stay was 10 (3–39) days. In our study, this time was 48.7 ± 23.7 days. We consider that the significant prolongation of hospital stay in our study is due to the underlying diseases of the patients (bone and joint infections), which require prolonged treatment. The mortality rate in DRESS syndrome has been reported to be approximately 10 %.[43] In our study, mortality did not occur during hospitalization and the first outpatient follow-up.

In vitro studies have revealed that a few drug-human leukocyte antigen (HLA)-binding interactions lead to activation of T cells.[44,45] They are classified according to 2 hypotheses: hapten and pharmacological interactions. With the development of diagnostic and predictive T-cell assays, direct drug HLA binding and formation of drug-protein adducts are important events for T-cell activation.[46] Protein-reactive drugs such as β-lactam antibiotics are known to activate T cells through direct non-covalent interactions with HLA or HLA-binding peptides, direct covalent modification of HLA-binding peptides, and covalent binding of non-HLA-related proteins.[44] Studies using synthetic stable and reactive (eg, nitroso-sulfamethoxazole) metabolites show that the metabolites activate T cells in the same ways.[47,48] Various drugs with different structural properties have also been shown to activate T cells through direct HLA-binding interaction. T cells and HLA type could not be performed due to limited sources in our study.

Anticonvulsant and antibiotic-associated DRESS differ in mechanism. The cytochrome P450 system converts several anticonvulsant drugs to arene oxide metabolites. Typically, they are detoxified to epoxide hydroxylase or glutathione transferase. These enzymes' genetic abnormalities result in decreased activity and an accumulation of toxic metabolites, which can directly impact organ systems and provoke immune-mediated responses.[49] There is no difference in clinical presentation, management, and treatment options between antibiotic and anticonvulsant-associated DRESS syndrome.

Patients with DRESS syndrome are at risk of developing systemic autoimmune sequelae that can occur from months to 4 years after the resolution of cutaneous manifestations and acute systemic involvement.[27] Autoimmune thyroiditis was found to be the most common sequela in the study.[50] Other autoimmune sequelae include diabetes mellitus, autoimmune hemolytic anemia, and alopecia.[50] Long-term follow-up of patients with DRESS is important for the development of autoimmune disorders. We did not detect any children with autoimmune diseases such as diabetes mellitus type 1, autoimmune hypothyroidism, systemic lupus erythematosus (SLE), systemic sclerosis, or adrenal insufficiency during the minimum of one year and maximum of six years of follow-up.

CONCLUSIONS

Bone and joint infections are common in childhood and typically resolved with appropriate antibiotic treatment and surgery. However, long-term antimicrobial therapy may be necessitated and sometimes lead to DRESS syndrome, a serious condition that should be considered due to its potential for morbidity and mortality. Clinicians should be aware of DRESS syndrome in children who develop fever and rash under long-term antibiotics and should check hematological and biochemical parameters to predict the severity of DRESS syndrome. In patients with persistent symptoms, steroids may be used to control the symptoms. This study is important because it shows that DRESS syndrome can develop, particularly in children who receive long-term antibiotic therapy, and that early diagnosis and treatment can reduce mortality and morbidity.

LIMITATIONS

This is a retrospective, single-center study. Some data may be missed due to retrospective

design. Another limitation was the lack of patch tests, intradermal tests, or lymphocyte transformation tests due to unavailability.

Abbreviations
DRESS, Drug reaction with eosinophilia and systemic symptoms; IV, intravenous; MRI, Magnetic resonance imaging; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RegiSCAR, Registry of Severe Cutaneous Adverse Reactions; PICU, Pediatric intensive care unit; CBC, Complete blood count; WBC, white blood cell; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; Hb, hemoglobin; PLT, platelet count; Pct, pro-calcitonin ESR; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; MPV, mean platelet volume; HLA, human leukocyte antigen

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Author contributions
All authors contributed to the study's conception and design. Sema Yildirim Arslan and Zumrut Sahbudak Bal performed material preparation, data collection, and analysis. Zumrut Sahbudak Bal wrote the first draft of the manuscript, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics and consent
This study was conducted with the approval of the Research Ethics Committee of Ege University, and the Turkish Ministry of Health approved the study (Ethical decision No. 21-6T/64). In addition, all parents or legal guardians of patients provided signed informed consent.

Authors' consent for publication
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