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REVIEW

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ABOUT COVER

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The primary aim of *World Journal of Transplantation* (*WJT*, *World J Transplant*) is to provide scholars and readers from various fields of transplantation with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJT mainly publishes articles reporting research results obtained in the field of transplantation and covering a wide range of topics including bone transplantation, brain tissue transplantation, corneal transplantation, descemet stripping endothelial keratoplasty, fetal tissue transplantation, heart transplantation, kidney transplantation, liver transplantation, lung transplantation, pancreas transplantation, skin transplantation, *etc.*.

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REVIEW

Voriconazole-associated periostitis: Pathophysiology, risk factors, clinical manifestations, diagnosis, and management

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Abstract

Voriconazole use has been associated with osteoarticular pain and periostitis, likely due to high fluoride content in the drug formulation. This phenomenon has been described primarily with high dosage or prolonged course of voriconazole therapy in immunocompromised and transplant patient populations. Patients typically present with diffuse bony pains associated with elevated serum alkaline phosphatase and plasma fluoride levels in conjunction with radiographic findings suggestive of periostitis. We provide a comprehensive review of the literature to highlight salient characteristics commonly associated with voriconazole-induced periostitis.

Key Words: Voriconazole; Periostitis; Fluoride; Fluorosis; Alkaline phosphatase

Core Tip: Voriconazole-induced periostitis is rare, and typically presents as bone pain following months of voriconazole treatment. Fluoride, present in voriconazole, deposits within the bony matrix causing bone pains and high serum alkaline phosphatase (ALP) with or without elevated plasma fluoride level. Evidence of periostitis is typically observed on skeletal imaging. Symptom relief occurs shortly after discontinuation of voriconazole, and normalization of serum ALP occurs in the following weeks to months. We herein discuss the pathophysiology and diagnosis of voriconazole-induced periostitis, its prevalence in different patient populations, and clinical outcomes.

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INTRODUCTION

A 19-year-old male presented with pain on his left foot that progressed to the right foot, both hips, and shoulders over a month. He was unable to bear weight on his feet due to excruciating pain. His past medical history was significant for hypertrophic obstructive cardiomyopathy and subsequent orthotopic heart transplantation approximately 1 year prior to presentation. The patient's post-transplant period was complicated by hypoxic respiratory failure due to invasive pulmonary aspergillosis, diagnosed by diffuse pulmonary infiltrates on computed tomography (CT) chest, elevated serum *Aspergillus* galactomannan enzyme immunoassay 4.8 (normal, < 0.5 optical density index), and growth of *Aspergillus flavus* from bronchoalveolar lavage culture. Combination therapy with voriconazole and micafungin was initiated given severity of the disease. Micafungin was discontinued once serum voriconazole trough concentration reached target therapeutic level > 1 mg/L (normal, 1-5.5 mg/L). The voriconazole dose was sequentially increased to 550 mg every 12 h which yielded serum voriconazole therapeutic trough concentration of 1.6 mg/L. The patient had received a total of approximately 11 mo of voriconazole prior to presentation with diffuse osteoarticular pain and tenderness.

Physical examination revealed significant point tenderness on elbows, shoulders, and ankles. Extensive dental fluorosis was noted in the patient's teeth as well (Figure 1). Significant laboratory findings included an elevated total serum alkaline phosphatase (ALP) level of 423 IU/L (normal, 39-117 IU/L) with high fractionated bone ALP of 308 IU/L (normal, 12-43 IU/L). Total bilirubin and transaminases were within normal limits. A serum voriconazole trough level was therapeutic target at 2 mg/L. Plasma fluoride level was normal at 0.4 mg/L (normal, 0.2-3.2 mg/L). Serum ionized calcium, vitamin D levels, and parathyroid hormone tests were all within normal limits. Multiple myeloma screen was negative. Suspicion of voriconazole-induced periostitis was entertained.

A skeletal survey was performed; it demonstrated thickening and elevation of periosteum on clavicle, humeri, and femur, suggestive of periostitis (Figure 2). A technetium-99m nuclear bone scan revealed diffuse abnormal radiotracer uptake over bilateral feet, proximal femurs, proximal humeri, and clavicles (Figure 3). In totality, these findings suggested a diagnosis of voriconazole-induced periostitis. The antifungal therapy was discontinued. Patient reported improvement of foot pain one week following the drug discontinuation. He was able to ambulate without assistance and tolerate physical therapy two weeks after discontinuation of voriconazole. The serum fluoride level became undetectable after voriconazole cessation for 3 wk. Normalization of serum ALP was achieved approximately one month after discontinuation of the drug. Fluoride deposits on the teeth, however, remained for a year after voriconazole discontinuation. No other antifungal agent was substituted and there has been no recurrence of invasive pulmonary aspergillosis to date.

BACKGROUND

Voriconazole is a triazole antifungal and is considered the treatment of choice for invasive aspergillosis[1]. It is also recommended for preemptive treatment or universal antifungal prophylaxis in patients with solid organ and hematopoietic stem cell transplant (HSCT)[1,2]. Although voriconazole is generally well tolerated, common adverse effects include visual and auditory hallucinations, peripheral neuropathy, hepatotoxicity (elevation of hepatic transaminase levels), phototoxicity, cutaneous cancers, cardiac arrhythmias from prolonged QTc interval, alopecia, nail changes, hyponatremia, and hyperkalemia[3,4]. Uncommon side-effect of drug-induced periostitis due to prolonged voriconazole therapy has been described in various case reports[3].

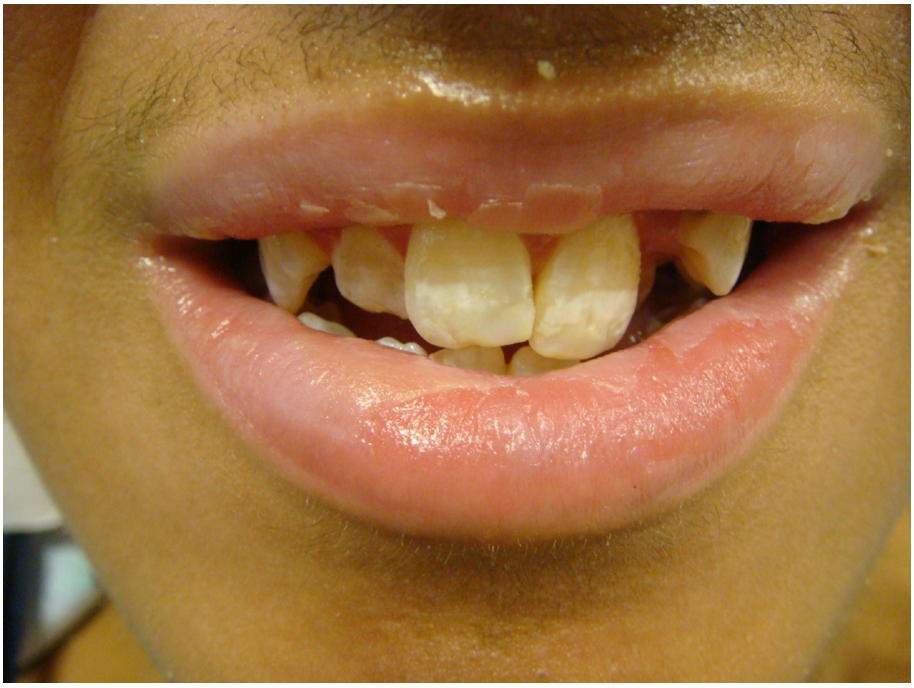

Figure 1 Whitish specks and discoloration, evidence of dental fluorosis, noted on the patient's teeth.

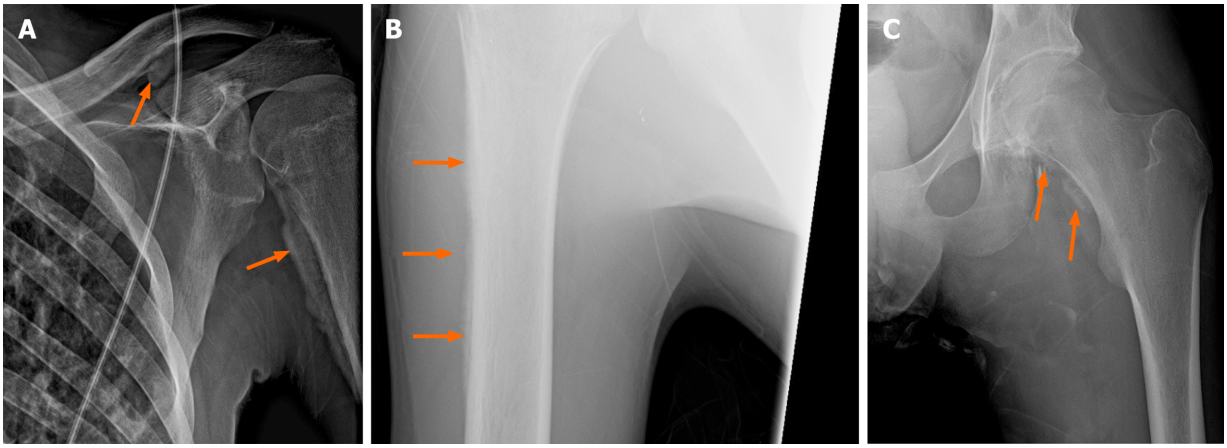

Figure 2 X-ray of bones showed evidence of skeletal fluorosis. A: Periosteal elevation (arrows) on the left clavicle and proximal left humerus; B: Fluffy periostitis (arrows) on the right humerus; and C: Periosteal reaction (arrows) on the proximal left femur.

We performed a comprehensive literature search in PubMed®, PubMed Central®, and Google Scholar®, using the words "fluconazole", "itraconazole", "voriconazole", "posaconazole", "isavuconazole", in combination with "bone pain", and "periostitis". The search retrieved all articles identifying association of periostitis with voriconazole. We did not find articles of periostitis from other triazoles. We obtained and reviewed the full texts of all articles and collected data for analysis.

DISCUSSION

A total of 89 cases of voriconazole-induced periostitis were reviewed (Table 1), including 2 pediatric patients, one 14-year-old lung transplant patient and one 3-mo-old stem cell transplant recipient[5-53]. Cases were published in the format of case reports (limited 1 case in an article, 19 articles)[7,9,10,16,19,22,25,27,30,32,34,37,38,40,42,43,45,47,51], case series (> 1 case in an article, 9 articles)[5,8,11,15,18,23,35,39,48], image section (12 articles)[12,13,17,21,28,31,33,36,46,49,50,53], photo quiz (1 article)[20], conference abstracts (5 articles)[6,14,24,26,29], letter to the editor (2 articles)[41,

Table 1 List of published cases of voriconazole-induced periostitis

Ref.	Total cases	Total daily dose, mg (number of cases) at time of diagnosis of periostitis	Duration of therapy, mo (number of cases)	Voriconazole trough (1-5.5 mg/L, normal range) at the time of diagnosis of periostitis	Immunocompromised state (number of cases)	Indication of voriconazole therapy (number of cases)	Serum ALP (normal range U/L)	Bone ALP isoenzyme, (normal range U/L)	Plasma fluoride level, (normal range)	Imaging performed	Sites of bony involvement	Resolution of symptoms following voriconazole discontinuation (number of cases)
[5]	5	400 (5)	15; 16; 26; 6; 21	N/A; N/A; N/A; N/A; N/A	Lung transplant (5)	Antifungal prophylaxis (5)	726 (31-103); 531; 404; 212; 111	263 (12-84); 300; N/A; N/A; N/A	N/A; N/A; N/A; N/A; N/A	X-ray, bone scan	Tibiae, fibulae, femurs, ulnae, radii, shoulders, scapulae, sacroiliac joints, ischia, humeri, clavicles, manubrium, ribs, ankles	Within 2 wk (1); Within 3 d (1); Within 1 wk (1); N/A (2)
[6]	1	N/A	1	N/A	Allogeneic stem cell transplant	Antifungal prophylaxis	Elevated	N/A	N/A	X-ray, MRI	Radius, metatarsals, fibulae, tibiae, calcaneus	Within 2 mo
[7]	1	400	31	N/A	Lung transplant	Antifungal prophylaxis	433 (40-125)	188 (20/71)	N/A	X-ray, CT scan, bone scan	hand phalanges, ribs	Within 1 mo
[8]	5	200 (1); N/A (4)	30 (1); N/A (4)	N/A	Lung transplant (5)	Antifungal prophylaxis (3); N/A (2)	N/A	N/A	N/A	X-ray, CT scan, bone scan	hand phalanges, clavicles, humerus, scapula, ribs, femur, knee, pubic rami, sacral iliac joint	N/A (5)
[9]	1	N/A	N/A	N/A	Lung transplant	N/A	N/A	N/A	N/A	X-ray	Multiple phalanges, ulnar shaft	Itraconazole replacement
[10]	1	1200	6	0.77	Acute myelogenous Leukemia	Disseminated *Fusarium* infection	525 (45-277)	351 (4-110)	24.3 (1-4 μmol/L)	X-ray, bone scan	Hands, forearms, humeri, femurs, pelvis, knee, feet	Improvement within 1 wk, complete resolution within 3 wk
[11]	6	400 (5); NA (1)	6; 7; 53; 16; 16; 21	N/A; 0.3; 2.8; 2.1; 1.0; 5.0	Heart transplant (1); Lung transplant (3); Kidney transplant (1); Stem cell transplant (1)	Invasive pulmonary aspergillosis (1); N/A (5)	521 (50-130); 361; 323; 243; 178; 229	N/A; 268 (12-42); N/A; N/A; N/A; N/A	20.7 (1-4 μmol/L); 27; 11.4; 7.5; 15.9; 13.2	X-ray, bone scan	Fingers, wrists, elbows, legs, feet, ribs	Within 2 mo (2); Itraconazole replacement, improvement within 1 month (1); N/A (3)
[12]	1	N/A	9	N/A	Heart transplant	Invasive Pulmonary aspergillosis	280	N/A	N/A	CT scan, bone scan	Ribs, sternum, humerus, forearm, femur, tibia, spine	N/A
[13]	1	400	1.5	N/A	Liver transplant	Cerebral *Aspergillus* infection	420 (30-120)	N/A	10.2 (1-4 μmol/L)	X-ray, bone scan	Femur, tibia, fibula, radius, ulna, ribs,	Amphotericin B replacement, rapid

											scapulae	resolution
[14]	1	N/A	12	N/A	Allogenic stem cell transplant	Invasive Aspergillus sinusitis and lung infection	475 (39-117)	152 (7-22)	N/A	X-ray, bone scan	Phalanges, elbows, humerus, femur	Within 1 wk
[15]	3	N/A (3)	3.3; 6; 7.5	N/A; N/A; N/A	Allogeneic stem cell transplant (3)	NA (3)	195 (35-104); 384; 202	N/A; N/A; N/A	N/A; 363 (<30 μg/L); 316	X-ray, CT scan, bone scan	Entire skeleton, spine, pelvis, hands, phalanges	Within 4 d (1); NA (2)
[16]	1	N/A	5	N/A	Heart transplant	Invasive pulmonary aspergillosis	304 (31-95)	90.8 (5.6-29 μg/L)	N/A	X-ray, CT scan, bone scan	Humerus, femur, ribs	Improvement within 2 wk
[17]	1	N/A	4	N/A	N/A	Fungal endophthalmitis	N/A	N/A	N/A	X-ray, bone scan	Radial and pretibial diaphysis, radius, ulna, tibia, fibula	Within 5 d
[18]	2	N/A (2)	5 (1); N/A (1)	N/A	Heart Transplant (1); Stem Cell Transplant (1)	Antifungal prophylaxis (heart transplant); NA (stem cell transplant)	304 (29-111); 245	N/A; N/A	N/A; N/A	X-ray, CT scan, bone scan	Ribs, clavicles, humeri, radii, ulnae, femurs, tibia, metacarpals, phalanges	N/A
[19]	1	400	11	N/A	Granulomatosis with Polyangiitis	Invasive pulmonary aspergillosis	464	N/A	N/A	X-ray, CT scan	Femur	Improvement within 2 d, resolution within 1 wk; posaconazole replacement
[20]	1	N/A	6	2.1	Chronic granulomatous disease	*Aspergillus* knee septic arthritis	380 (54-130)	N/A	133 (< 20 μg/L)	X-ray, bone scan	Ribs, clavicles, humerus, tibia	Posaconazole replacement, improvement within 2 wk
[21]	1	400	9	N/A	Lung transplant	Pulmonary aspergillosis	359 (40-150)	N/A	N/A	CT	Scapulae, ribs, radius, ulna	N/A
[22]	1	600	4	3	Mixed connected tissue disorder (overlap syndrome)	Pulmonary aspergillosis	1060 (115-359)	89.3 (3.8-22.6 μg/L)	24.9 (1-4 μmol/L)	CT, MRI, bone scan	Scapulae, ribs, femurs	Within 3 wk
[23]	21	800; 500; 600; 1300; 700; 800; 500; 700; 500; 700; 700; 1100; 900; 700; 900; 700; 900; 900; 800; 700; 1000	7; 7.3; 5.5; 5; 5.5; 6.6; 4.9; 5.3; 4.6; 5; 4; 4.8; 5.5; 5.5; 6.3; 5.9; 7.5; 6.8; 5; 4.7	1.1; 2.3; 3.3; 4; 1.4; 2.6; 3; 3.8; 1.6; 1.5; 5.4; 1.3; 4.2; 1.5; 0.5; 1.5; 3.2; 2.5; 0.5; 2.5; 2	Malignancy (2); DM (2); CKD (1); None (16)	Exserohilum rostratum, or *Aspergillus fumigatus* meningitis (contaminated methylprednisolone acetate injection)	114 (27-120); 281; 362; 362; 452; 226; 168; 221; 97; 155; 202; 848; 208; 238; 123; 277; 442; 244; 231; 256; 228	N/A	11.05 (< 5.26 μmol/L); 10.53; 10.0; 14.74; 14.74; 13.16; 0.0; 12.63; 12.11; 14.21; 18.95; 16.84; 14.21; 10.53; 13.69; 8.42; 17.90; 8.95; 21.06; 10.53; 14.21	Bone scan	Radius, ulna, tibia, fibula, clavicle, scapula, femur, ribs	2 wk to 5 mo (8); residual pain (2); 5/10 with symptom improvement in 2-8 wk following dose reduction
[24]	1	N/A	N/A	N/A	Lung transplant	*Cladosporium*	elevated	N/A	N/A	X-ray	Hands, knees, feet	Itraconazole

						pneumonia						replacement, improvement over hospital course
[25]	1	N/A	12	N/A	Acute Myelogenous Leukemia	Fungal sinusitis	N/A	N/A	N/A	X-ray, CT scan, MRI, Bone scan	Clavicle, humerus, rib	Less than 2 wk
[26]	1	800	3	4.1	Liver Transplant	*Aspergillus* brain abscess	N/A	N/A	16.3 (0.3-2.2 μmol/L)	X-ray	Radius, humerus, scapulae, ribs, appendicular skeleton	N/A
[27]	1	8 mg/kg	36	N/A	Mixed connective tissue disease	Extra-pulmonary histoplasmosis	585 (35-104)	N/A	N/A	X-ray, SPECT/CT scan, bone scan	Radius, ulna, scapulae, femur, shoulders, spine, knees, ankle	N/A
[28]	1	400	4	N/A	Allogeneic stem cell transplant	Fungal pneumonia	N/A	N/A	N/A	Bone scan	Clavicle, rib, hip, femur, tibia, fibula	Within 4 d
[29]	1 (14-year-old)	N/A	N/A	N/A	Lung transplant	N/A	N/A	N/A	N/A	X-ray, Bone scan	Phlanges, metatarsals, tibia and long bones, clavicles, scapula, sternum, pelvic bones	N/A
[30]	1	400	5	N/A	Lung transplant	Antifungal therapy for abnormal bronchoalveolar lavage	332 (no normal range)	N/A	N/A	X-ray, MRI	Hips	Itraconazole replacement; improvement within 2 wk, resolution within 4 wk
[31]	1	600	10	N/A	T-cell prolymphocytic leukemia	Cerebral histoplasmosis	200 (25-100)	N/A	N/A	X-ray, Bone scan	Clavicles, ribs, tibia, fibula	Within 2 d
[32]	1	N/A	2	3.9	Liver transplant	*Scedosporium* brain abscess	N/A	N/A	Elevated	N/A	N/A	Posaconazole replacement, resolution
[33]	1	400	N/A	N/A	Heart transplant	Pulmonary aspergillosis	323 (40-115)	N/A	0.15 (0.02-0.08 mg/dL)	X-ray	Humerus	Improvement within 5 d, resolution within 2 mo
[34]	1	800	3	4.1	Liver transplant	*Aspergillus* brain abscesses	N/A	N/A	16.3 (0.3-2.2 μmol/L)	X-ray, Bone scan	Radius, humerus shafts, scapulae	Resolved rapidly after cessation of voriconazole
[35]	3	400; 400; 400	3.3 (1); 6.5 (1) N/A (1)	NA (3)	Lung transplant; stem cell transplant; liver transplant	Fungal infection (1); fungal pneumonia (2)	215 (0-140); 181-501; 500-1000	N/A	N/A	CT scan	Sternum, vertebrae, ribs, scapulae, appendicular skeleton, ribs	N/A
[36]	1	N/A	N/A	N/A	Lung transplant	Pulmonary aspergillosis	277 (no normal range)	N/A	N/A	Bone scan, FDG-PET, CT scan	Ribs, clavicle, acetabulum, hips	N/A

[37]	1 (3-mo-old infant)	N/A	4.5	N/A	Stem cell transplant	Disseminated aspergillosis	2,416 (95-380)	1,581 (43-208)	23.8 (1-4 μmol/L)	X-ray	Femur, tibia, fibula,	Posaconazole replacement; improvement within 2 d, resolution within 1 wk
[38]	1	N/A	36	N/A	0	*Candida glabrata* abdominal aortic graft infection	N/A	129 (0-20 μg/L)	23.6 (1-4 μmol/L)	X-ray, Bone scan	Ribs, humeri, tibiae, Elbow, hand, carpometacarpal joint,	Within 3 wk
[39]	2	800 (1); NA (1)	2 (1); 7 (1)	N/A (2)	Liver transplant (1); heart transplant (1)	*Scedosporium* brain abscess (2)	N/A	N/A	> 24 (1-4 μmol/L); 26	X-ray, Bone scan	Sternoclavicular joints, elbows, wrists, hands, knees, ankles, feet, tibia, fibula, bilateral hip, ribs, spine, scapulae, clavicles acetabula femur, metatarsals	Posaconazole replacement, improvement in several weeks (1)
[40]	1	N/A	6	Therapeutic	Stem cell transplantation	Invasive fungal lung infection	341 (40-125)	N/A	N/A	MRI, X-ray	Hand phalanges	Improvement within 1 wk
[41]	1	200	4.4	N/A	Stem cell transplantation	N/A	normal	N/A	N/A	X-ray, CT scan, Bone scan	Tibiae, finger phalanges, malleolus	Itraconazole replacement, resolution within 4 mo
[42]	1	600	10	4	Granulomatosis with polyangiitis	pulmonary aspergillosis	> 1,000 (< 130)	N/A	278 (< 50 μg/L)	X-ray, CT scan, Bone scan	Phlanges, radius, ulna, metacarpals, tibia, ribs, femur	Rapid improvement
[43]	1	400	48 mo	N/A	Lung transplant	Pulmonary aspergillosis	673 (35-125)	203 (0-20 μg/L)	N/A	X-ray, MRI, Bone scan	Metacarpals, phalanges, midfeet, femurs, pubic bone, acetabula, radius, ulna, humeral heads, ribs, clavicles, skull	Improvement within 3 mo
[44]	1	800	3	3.22	Lung transplant	N/A	4.71 (0.92-2.15 microkat/L)	N/A	N/A	Bone Scan	Fingers, humeri, scapula, elbows, femurs, tibiae, ribs	Within 5 d
[45]	1	600	7	N/A	DM	Aspergillus skull bone osteomyelitis	N/A	N/A	N/A	X-ray, Bone scan	Extremities, ribs, and spine	Resolved
[46]	1	N/A	N/A	N/A	Stem cell transplant	N/A	N/A	N/A	N/A	X-ray, CT, bone scan	Clavicle, humeri, scapulae, ribs, femurs	N/A
[47]	1	700	3	1.9	Renal transplant	Pulmonary aspergillosis	N/A	N/A	68 (1-4 μmol/L)	SPECT, bone scan	Knees, clavicles	Within 48 h
[48]	2	NA (1); 600 (1)	3 (1); 17 (1)	N/A; N/A	Lung transplant; lung transplant	Antifungal prophylaxis	N/A; N/A	N/A; N/A	N/A; N/A	X-ray, bone scan	Fingers, toes, ulnar bones, humeri, shoulders, femurs,	Within 1 wk; Within 10 d

											tibia	
[49]	1	1200	4	Within recommended range (no value provided)	Stem cell transplant	Pulmonary aspergillosis	457 (40-130)	N/A	N/A	SPECT	Skull bones, pelvic bones, femurs, humerus	Switched to Posaconazole; Within 3 wk
[50]	1	N/A	96	N/A	Lung transplant	Antifungal Prophylaxis	724 (34-123)	N/A	N/A	X-ray	Hands, wrists	> 7 mo
[51]	1	1200	4	9.9	0	Invasive aspergillosis (lung, brain)-post-influenza and pneumococcal infection	1900 (no normal range)	N/A	N/A	Single-photon emission CT	Extremities	Resolved
[52]	1	100	6	N/A	0	Aspergillus sinusitis and brain abscess	1495 (4-147)	N/A	5.3 (1-4 μmol/L)	X-ray, bone scan	Hands, ankles, and foot	2 mo
[53]	1	400	48	N/A	Stem cell transplant	Antifungal Prophylaxis	144 (35-104)	N/A	N/A	X-ray, bone scan	Tibia, fibula	N/A

ALP: Alkaline phosphatase; MRI: Magnetic resonance imaging; CT: Computer tomography; FDG-PET: β-2-[18F]-Fluoro-2-deoxy-D-glucose-positron emission tomography; DM: Diabetes mellitus.

44], and clinicopathologic conference (1 article)[52]. One case report was published in both Danish and English, and it was included in our analysis because there was ample amount of information in English[51]. Table 1 summarizes those 89 cases with relevant patients' baseline characteristics, voriconazole daily dose, duration of voriconazole therapy, voriconazole trough concentration, indication of voriconazole therapy, immunocompromised status, serum ALP and its bony fraction, plasma fluoride level, imaging study, and clinical outcomes. Not all information was available in reported cases, especially cases published in image section of the journal and conference abstracts likely due to limitation of word counts per the journal and conference requirements.

Based on the high incidence of voriconazole-induced periostitis in certain patient populations, we have categorized the reported patients into 3 major groups, namely solid organ transplant (SOT) patients, hematologic malignancy and HSCT patients, and immunocompetent hosts. Patients with malignancy[23], diabetes mellitus[23,45], chronic kidney disease[23], chronic granulomatous disease[20], granulomatosis with polyangiitis[19,42], and mixed connective tissue disease[22,27] were not included in the immunocompetent patient category.

The vast majority of voriconazole-associated periostitis cases have been reported in SOT recipients (n = 40, 45%)[5,7,8,11-13,16,18,21,24,26,29,30,32-36,39,43,44,47,48,50], immunocompetent hosts (n = 19, 21.34%)[23,38,51,52], hematologic malignancy and HSCT patients (n = 18, 20.3%)[6,10,11,14,15,18,25,28,31,35,37,40,41,46,49,53]. It is followed by autoimmune diseases (n = 4, 4.44%), including 2 patients with granulomatosis with polyangiitis[19,42], and 2 patients with mixed connective tissue disease [22,27]. One patient (1.12%) had underlying primary immunodeficiency disease

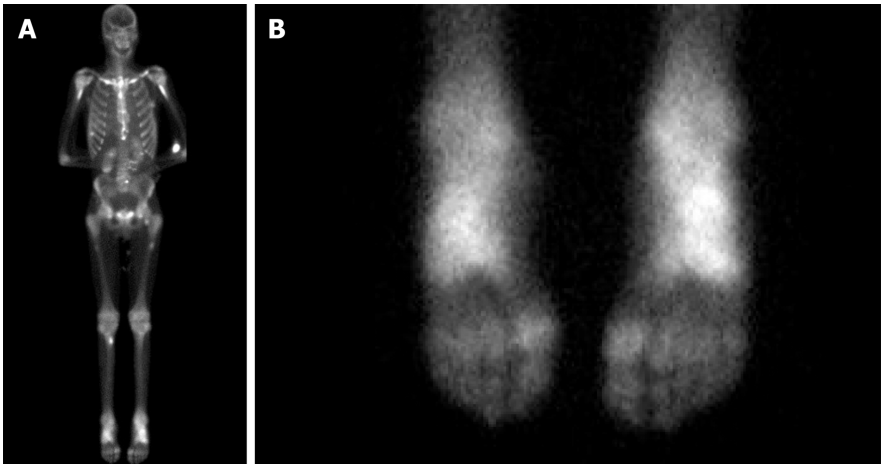

Figure 3 Whole body nuclear bone scan. Increased radiotracer uptake (bright white spots) on clavicles, humeri, and femurs (A), as well as feet (B).

(chronic granulomatous disease) and developed periostitis on voriconazole therapy for *Aspergillus* septic arthritis of the knee[20]. Two patients (2.22%) with underlying diabetes mellitus, 2 patients (2.22%) with unspecified malignancy, and 1 patient (1.12%) with chronic kidney disease had voriconazole-induced periostitis while being treated for *Exserohilum rostratum* or *Aspergillus fumigatus* meningitis from contaminated methylprednisolone epidural steroid injection[23]. One patient (1.12%) with diabetes mellitus complicated with periostitis after 7 mo of voriconazole therapy for *Aspergillus* skull bone osteomyelitis[45]. One patient's (1.12%) details did not include the immune status of the host[17].

Table 2 summarizes the median voriconazole daily dose with inter-quartile range, median duration of therapy with inter-quartile range, and medial voriconazole trough level in each major patient category. The daily voriconazole dose was reported in 59 cases, consisting of 24 SOT patients[5,7,8,11,13,21,26,30,33-35,39,43,44,47,48], 8 hematologic malignancy and HSCT recipients[10,11,28,31,35,49,53], 18 immunocompetent hosts[23,51,52], and 9 others[19,22,23,42,45]. The duration of voriconazole therapy was described in 77 cases (30 SOT patients[5,7,8,11-13,16,18,21,26,30,32,35,39,43,44,47,48,50], 16 HSCT recipients[6,10,11,14,15,28,31,35,37,40,41,49,53], 18 immunocompetent hosts[23,38,51,52], and 13 others[19,20,22,23,27,42,45]. The voriconazole trough level was mentioned in 38 cases, including 9 SOT patients[11,26,32,34,44,47], 2 HSCT recipients[10,11], 17 immunocompetent hosts[23,51], and 10 others[20,22,23,42].

Fluoride metabolism, voriconazole metabolism, and pathophysiology of voriconazole-associated periostitis

Fluoride is an inorganic anion of fluorine, and its sources include ingestion of water, salt, sugar, and milk, or topical from toothpastes and mouth rinses[54]. The benefits of fluoride to humans consist of anti-dental caries formation and enhancement of bone strength[55,56]. About 80%-90% of ingested fluoride is absorbed in the stomach and small intestine, and the unabsorbed fluoride is excreted in the feces[54]. A majority of absorbed fluoride is distributed to bone and dental enamel[54,57]. The kidneys excrete 60% of daily ingested fluoride in persons with normal renal function[54,58].

Voriconazole is a broad-spectrum triazole antifungal medication. The oral bioavailability of voriconazole is estimated to be 96%[4]. The pharmacokinetics of voriconazole is non-linear due to saturation of its metabolic pathway[4]. The hepatic cytochrome P450 enzyme, predominantly CYP2C19, is responsible for voriconazole metabolism. Due to CYP2C19 enzyme genetic polymorphisms, a person with a rapid CYP2C19 enzyme metabolizer, for example, would require a higher dose of voriconazole to achieve therapeutic drug concentration[4,59]. Less than < 2% of the absorbed voriconazole is excreted unchanged in the urine[4].

Triazole antifungal agents contain varying amounts of fluorine (Figure 4). Fluconazole, posaconazole, and isavuconazole are difluorinated triazoles while itraconazole does not have fluorine content. Voriconazole contains three fluorine atoms, and a 400-mg dose of voriconazole contains a substantial 65 mg of fluoride[11]. In comparison, the fluoride content of the municipal tap water is 1 mg per liter[60]; and, thus daily fluoride consumption from municipal tap water has been estimated at only 2 to 4 mg per day[10,60].

Table 2 List of reporting cases with voriconazole median daily dose, median duration of therapy, and its median trough concentration in different major patient groups

Type of patients	Median voriconazole daily dose, (interquartile range), and number of cases	Median duration of voriconazole therapy in months, (interquartile range), number of cases months	Median voriconazole trough concentration in mg/L, number of cases
All patients	600 mg, (400-800 mg), 59 patients[5,7,8,10,11,13,19,21-23,26,28,30,31,33-35,42-45,47-49,51-53]	6 mo, (4.6 – 10 mo), 77 patients[5-8,10-16,18-23,26-28,30-32,35,38-45,47-53]	2.4 mg/L, 38 patients[10,11,20,22,23,26,32,34,42,44,47,51]
Solid organ transplants	400 mg, (400-450 mg), 24 patients[5,7,8,11,13,21,26,30,33-35,39,43,44,47,48]	7 mo (3 – 17 mo), 30 patients[5,7,8,11-13,16,18,21,26,30,32,35,39,43-44,47,48,50]	3.22 mg/L, 9 patients[11,26,32,34,44,47]
Hematologic malignancy and hematopoietic stem cell transplants	400 mg, (400-750 mg), 8 patients[10,11,28,31,35,49,53]	6 mo (4.3–10.5 mo), 16 patients[6,10,11,14,15,28,31,35,37,40,41,49,53]	0.885 mg/L, 2 patients[10,11]
Immunocompetent hosts	700 mg, (700-875 mg), 18 patients[23,51,52]	5.6 mo, (4.9–6.8 mo), 18 patients[23,38,51,52]	2.5 mg/L, 17 patients[23,51]

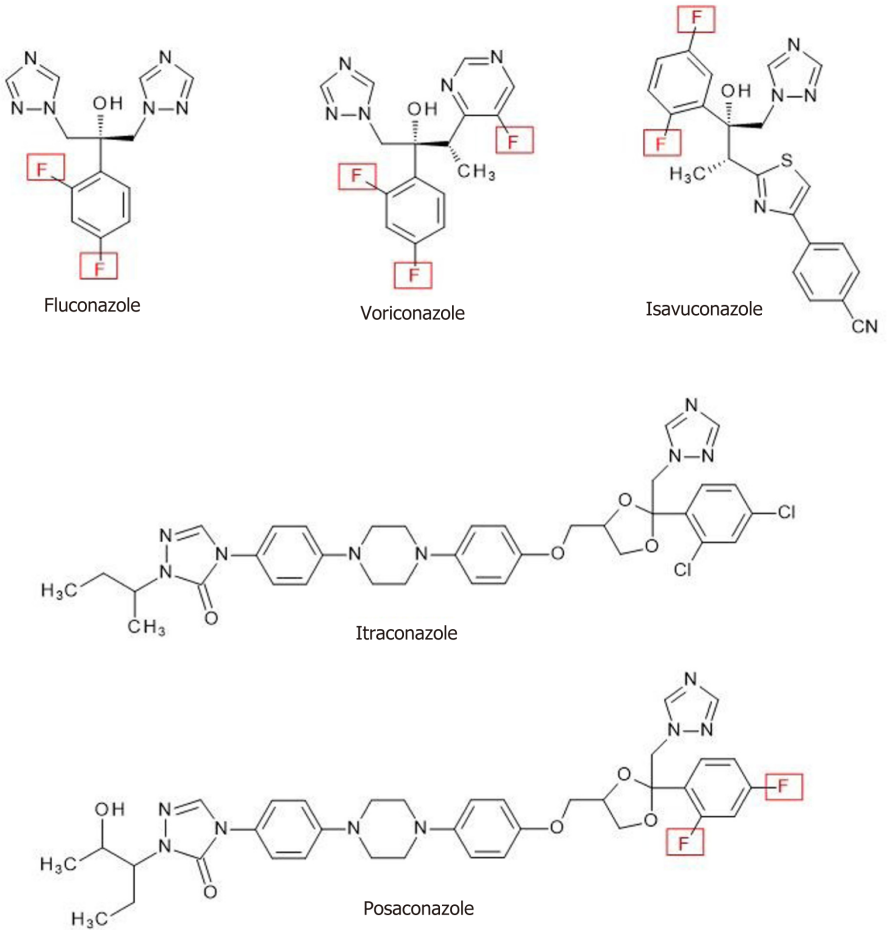

Figure 4 Chemical structures of triazole antifungal medications (fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole). "F" stands for fluorine atom (with permission and courtesy from Dr. Harrold, Division of Pharmaceutical, Administrative and Social Sciences; Duquesne University School of Pharmacy).

Absorbed excess fluoride is incorporated into the crystal structure of bony matrix called hydroxyapatite, forming fluorapatite[61]. Unlike normal calcium hydroxyapatite, high fluroapatite deposit causes disorganized osteoblastic reaction, resulting in periosteal thickening or ossification (seen as periosteal elevation on X-ray), exostosis, and osteosclerosis, a condition known as skeletal fluorosis[54]. Prolonged stimulation of osteoblast activity (evidenced by increased radiotracer uptake on the nuclear bone scan) results in generalized bone pain, exostosis, fractures from increased bony brittleness, a high total serum and bony ALP level, and elevated plasma fluoride concentration[62,63].

Some authors proposed there is a fluoride-independent mechanism that could cause periostitis from voriconazole drug per se[64]. *In vitro*, voriconazole exerts a direct drug effect and increases expression of cytokines, vascular endothelial growth factor and platelet-derived growth factor. Those cytokines, in turn, augment human osteoblast activity. Free fluoride levels in culture supernatants of osteoblasts exposed to voriconazole were measured and they were within normal range, indicating a possible direct voriconazole drug-induced periostitis[64]. However, this hypothesis has not been widely accepted.

The appendicular skeletons (bones of the shoulder girdle, pelvis bones, upper limbs and lower limbs) are mainly affected. In axial skeleton, only ribs are notably involved. High concentration of fluoride deposits may occur on dental enamel, causing dental fluorosis, which appears as white streaks or specks as seen in our patient (Figure 1)[54].

Voriconazole-induced periostitis in the SOT recipients

Among 40 patients with SOT, lung transplants accounted for 26 patients (65%)[5,7-9,11,21,24,29,30,35,36,43,44,48,50], followed by 6 liver transplants (15%)[13,26,32,34,35,39], 6 orthotopic heart transplants (15%)[11,12,16,18,33,39], and 2 kidney transplants (5%)[11,47]. It is not unexpected that majority of these cases occurred in lung transplant recipients as invasive pulmonary fungal infection is most commonly seen post-lung transplantation[2]. One third of lung transplant patients (n = 6, 23%) developed periostitis on the treatment dose regimen of voriconazole[21,24,30,35,36,43]. Indication of voriconazole therapy was not mentioned in 8 patients (31%) of lung transplant recipients with periostitis[8,9,11,29,44]. Interestingly, 12 (46%) out of 26 lung transplant patients developed voriconazole-related periostitis while receiving low daily dose (200-400 mg) of voriconazole prophylaxis as the use of antifungal prophylaxis with this agent is a common practice in lung transplant recipients[2,5,7,8,48,50,65].

Twenty-four SOT patients reported daily voriconazole doses, and the median daily dose was 400 mg (range 200-800 mg) with the interquartile range of 400-450 mg[5,7,8,11,13,21,26,30,33-35,39,43,44,47,48]. Duration of therapy was reported in 30 SOT patients; the median duration was 7 mo (range 1.5-96 mo) with the interquartile range of 3-17 mo[5,7,8,11-13,16,18,21,26,30,32,35,39,43,44,47,48,50].

Voriconazole trough levels were described in 9 out of 40 SOT patients with periostitis[11,26,32,34,44,47], and trough concentrations were reported with the normal range (1-5.5 mg/L) in 8 patients[11,26,32,34,44,47]. One patient's voriconazole trough level was sub-therapeutic at 0.3 mg/L while receiving a total daily dose of 400 mg for 7 mo[11]. The median voriconazole trough level was 3.22 mg/L (range 0.3-5.0 mg/dL). Plasma fluoride levels were described in 13 SOT recipients, and all were elevated[11,13,26,33,34,39,47].

Voriconazole-induced periostitis in the immunocompetent hosts

The second most common patient population reported in the literature with voriconazole-related periostitis is in patients with apparent immunocompetent status (n = 19, 21.32%)[23,38,51,52]. Sixteen out of 19 patients with periostitis were observed in patients with *Exserohilum rostratum* or *Aspergillus fumigatus* meningitis from contaminated methylprednisolone epidural steroid injection[23]. Eighteen patients reported daily voriconazole dose and duration of voriconazole therapy[23,51,52] while 17 patients included voriconazole trough levels in their reporting[23,51]. Among 19 immunocompetent patients, the median daily dose of voriconazole was 750 mg (range 500-1300 mg) with the interquartile range of 700-875 mg[23,38,51,52], which was notably higher than doses observed in SOT recipients presenting with periostitis (Table 2). These data are likely skewed by large number of fungal meningitis cases in this patient group[23]. Higher voriconazole target troughs (2-6 mg/L) are commonly recommended for the treatment of the central nervous system fungal infection[66]; and, higher voriconazole dosages are typically required to attain the target voriconazole troughs. The median voriconazole trough level was 2.5 mg/L (range 0.5-9.9 mg/L), and the median duration of voriconazole therapy was 5.3 mo (range 4-7.5 mo) with the interquartile range of 4.9-6.8 mo (Table 2). All cases, except 1 patient, had elevated blood fluoride concentration at least twice above the normal range[23,38,52]. Compared to the SOT patients with voriconazole-induced periostitis, the higher median dose of voriconazole with shorter median duration of therapy was noted in patients without underlying apparent immunocompromising condition (Table 2).

Voriconazole-induced periostitis in hematologic malignancy and HSCT patients

In this category, there were a total of 18 patients (20.3%, out of 89 total patients)

identified, comprising 3 patients with hematologic malignancy and 15 HSCT recipients [6,10,11,14,15,18,25,28,31,35,37,40,41,46,49,53]. One of the stem cell transplant patients was a 3-mo-old infant[37]. Notably, less than half of the cases (8 patients) reported the daily dose of voriconazole[10,11,28,31,35,49,53] whereas more than two-third of cases (16 patients) described the duration of voriconazole therapy[6,10,11,14,15,28,31,35,37,40,41,49,53]. The median dose was 400 mg (range 200-1200 mg) with the interquartile range of 400-750 mg (Table 2). The median duration of voriconazole therapy was 6 mo (range 1-48 mo) with the interquartile range of 4.3-10.5 mo (Table 2). Only 2 cases reported voriconazole trough concentrations (0.77 mg/L and 1.0 mg/L) at the time of diagnosis of periostitis[10,11]. Two other cases stated voriconazole trough levels within the recommended therapeutic range, without reporting specific values[40,49]. Plasma fluoride levels were only available in 5 patients, and were all 5-10 times above the normal range[10,11,15,37].

Upon evaluation of these 3 largest groups of patients (SOT, immunocompetent patients, and HSCT), there seems to be a trend that suggests higher daily dose of voriconazole (more than 600 mg daily dose) and longer duration of therapy (more than 5.6 mo) may pose a higher risk of developing periostitis (Table 2). Voriconazole-induced peritonitis has been reported with total daily doses as low as 100 mg, highlighting a particular relationship with prolonged exposure of voriconazole and periostitis[52]. Due to genetic CYP2C19 polymorphisms and the potential for various drug-drug interactions, voriconazole therapeutic drug monitoring is commonly performed[59]. Efficacy and safety data suggest optimal target voriconazole trough levels of 1-5.5 mg/L[2,66-68].

As previously noted, patients who rapidly metabolize voriconazole due to CYP2C19 genetic polymorphisms may require higher doses to maintain target trough levels, subsequently exposing patients to higher levels of fluoride intake. Likewise, it has been reported that significantly higher daily and cumulative voriconazole doses were observed in patients with voriconazole-induced periostitis[23]. In our review, patients displayed either therapeutic or sub-therapeutic voriconazole trough levels. These data suggest that voriconazole trough levels do not need to be supra-therapeutic to develop periostitis, and the drug levels alone are not a predictor of periostitis incidence.

All except one patient in our analysis displayed significantly elevated plasma fluoride concentration, indicating its potential utility for the diagnosis of periostitis[10,11,13,15,20,22,23,26,32-34,37-39,42,47,52]. Symptomatic patients with skeletal pain along with plasma fluoride levels greater than 8 μmol/L (normal, < 5.26 μmol/L) has been previously reported as a highly sensitive (95%) and specific (100%) measure for periostitis[23]. Generalization of this finding may be limited as it was a small study and variable normal values of plasma fluoride concentration were used in reported cases (Table 1). Thus, clinicians should observe if the normal value of plasma fluoride from the local laboratory is the same as that in the study. It is also important to note that no correlation between voriconazole drug levels and plasma fluoride levels has been found[69].

Other triazole antifungal medications and periostitis

Itraconazole has no fluorine atom in drug formulation (Figure 4). There were cases where voriconazole was replaced by itraconazole with resolution of symptoms[9,11,24,30,41]. Posaconazole is a difluorinated triazole and it yields around 21.7 mg of fluoride per 400-mg dose[10], 3 times lower than that of voriconazole. Posaconazole was not found to cause fluoride elevations in a small hematologic malignancy patient cohort [15]. Some patients with voriconazole-associated periostitis had successfully transitioned to posaconazole without recurrence of similar symptoms[19,20,32,37,39,49]. It is unclear how much fluoride content is available in a 186 mg-tablet of isavuconazole. There are only 2 fluorine atoms in isavuconazole, and thus, it may be safely assumed that the total fluoride content in isavuconazole is less than that of voriconazole. There have not been any published cases of periostitis associated with itraconazole, posaconazole or isavuconazole therapy. Our patient received 1100 mg per day of voriconazole, nearly 180 mg of fluoride daily (approximately 60 times normal daily fluoride consumption from water) for an 11-mo time period until the time of diagnosis of periostitis.

Diagnosis of voriconazole-induced periostitis

The most common clinical manifestation is localized diffuse bony pain from skeletal fluorosis, mainly affecting fingers, wrists, elbows, shoulders, clavicles, toes, ankles, knees, and hips. Thoracic rib pain can be present if fluorosis involves ribs. Either high dose voriconazole or prolonged duration of therapy would heighten the clinical suspicion of periostitis. Total serum ALP levels and its bony fraction, if measured, are

consistently elevated upon diagnosis of periostitis. Voriconazole trough concentrations are usually within the normal range (1-5.5 mg/L). High plasma fluoride level would strongly support the diagnosis of periostitis; but, normal or low plasma fluoride level does not exclude it[23]. The X-ray of bones typically demonstrates periosteal reaction with elevation and thickening. The technetium 99m-nuclear bone scan shows high radiotracer uptake due to increased osteoblastic action. Typically, skeletal X-ray and nuclear bone scan are sufficed in diagnosis of periostitis[70]. In some reported cases, advanced imaging modalities, such as single-photon emission CT, fluorodeoxy-glucose-positron emission tomography, and magnetic resonance imaging were utilized [22,25,27,30,36], likely because of elusive etiology of periostitis and less awareness of voriconazole as the cause of periostitis. Those advanced imaging studies are, though, not recommended to be the first choice of imaging study[70]. Discontinuation of voriconazole usually results in rapid resolution of symptoms. No mortality from voriconazole-induced periostitis has been reported.

Summary

In summary, based on extensive reported cases, several observations can be made regarding voriconazole-induced periostitis: (1) Immunocompromised patients constitute majority of the cases; (2) Generalized osteoarticular pain is a cardinal clinical symptom; (3) White streaks or specks on teeth (dental fluorosis) can be seen in some patients; (4) Higher voriconazole dose or the longer duration of voriconazole therapy increases the risk of voriconazole-induced periostitis; (5) Patients on antifungal prophylactic dosing with voriconazole are not spared and they can develop periostitis; (6) Elevation of serum ALP with normal transaminases and bilirubin is a major laboratory indicator for initial clinical suspicion of periostitis in patients with bone pain on voriconazole therapy; (7) Voriconazole trough levels are typically within the therapeutic range; (8) High plasma fluoride levels assist in diagnosis of periostitis (skeletal fluorosis); (9) X-ray and nuclear bone scans are commonly utilized to localize periosteal reaction/thickening and increased bone turnover activity, respectively; (10) Complete and rapid resolution of symptoms is achieved on cessation of voriconazole therapy; and (11) Safe transition to itraconazole, posaconazole, or isavuconazole is recommended, if clinically needed, since there have not been reported cases of periostitis from other triazole antifungal medications.

CONCLUSION

Voriconazole-induced periostitis occurs mainly in post-transplant period following high dose (median 600 mg daily) or prolonged course of voriconazole therapy (median 5.6 mo). Key diagnostic parameters include diffuse bone pain, white specks on the teeth, elevated serum ALP and plasma fluoride levels, with positive nuclear bone scan and radiology findings. Removal of offending agent, voriconazole in this case, would be the mainstay of therapy with resolution of bone pain. Due to lack of fluoride in itraconazole and low fluoride content in posaconazole or isavuconazole, voriconazole may be substituted by other appropriate triazole antifungal drugs if clinically indicated.

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REFERENCES

1 **Patterson TF**, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, Kontoyiannis DP, Marr KA, Morrison VA, Nguyen MH, Segal BH, Steinbach WJ, Stevens DA, Walsh TJ, Wingard JR, Young JA, Bennett JE. Executive Summary: Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect*

Dis 2016; **63**: 433-442 [PMID: 27481947 DOI: 10.1093/cid/ciw444]
2 **Husain S**, Camargo JF. Invasive Aspergillosis in solid-organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant* 2019; **33**: e13544 [PMID: 30900296 DOI: 10.1111/ctr.13544]
3 **Levine MT**, Chandrasekar PH. Adverse effects of voriconazole: Over a decade of use. *Clin Transplant* 2016; **30**: 1377-1386 [PMID: 27581783 DOI: 10.1111/ctr.12834]
4 **Vfend [package insert]**. New York: Pfizer, Inc; Revised Jan, 2021. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021266s047,021267s057,021630s036lbl.pdf
5 **Wang TF**, Wang T, Altman R, Eshaghian P, Lynch JP 3rd, Ross DJ, Belperio JA, Weigt SS, Saggar R, Gregson A, Kubak B. Periostitis secondary to prolonged voriconazole therapy in lung transplant recipients. *Am J Transplant* 2009; **9**: 2845-2850 [PMID: 19845595 DOI: 10.1111/j.1600-6143.2009.02837.x]
6 **Pearce C**, Papadopoulous E, Sokolof J. Diffuse Musculoskeletal Pain After Prophylactic Voriconazole Therapy in a Bone Marrow Transplant Patient: A Case Report. *PM&R* 2010; **2**: S20 [DOI: 10.1016/j.pmrj.2010.07.058]
7 **Ayub A**, Kenney CV, McKiernan FE. Multifocal nodular periostitis associated with prolonged voriconazole therapy in a lung transplant recipient. *J Clin Rheumatol* 2011; **17**: 73-75 [PMID: 21169844 DOI: 10.1097/RHU.0b013e31820aff12]
8 **Chen L**, Mulligan ME. Medication-induced periostitis in lung transplant patients: periostitis deformans revisited. *Skeletal Radiol* 2011; **40**: 143-148 [PMID: 20652242 DOI: 10.1007/s00256-010-0997-y]
9 **Lustenberger DP**, Granata JD, Scharschmidt TJ. Periostitis secondary to prolonged voriconazole therapy in a lung transplant recipient. *Orthopedics* 2011; **34**: e793-e796 [PMID: 22049971 DOI: 10.3928/01477447-20110922-35]
10 **Skiles JL**, Imel EA, Christenson JC, Bell JE, Hulbert ML. Fluorosis because of prolonged voriconazole therapy in a teenager with acute myelogenous leukemia. *J Clin Oncol* 2011; **29**: e779-e782 [PMID: 21969513 DOI: 10.1200/JCO.2011.35.9604]
11 **Wermers RA**, Cooper K, Razonable RR, Deziel PJ, Whitford GM, Kremers WK, Moyer TP. Fluoride excess and periostitis in transplant patients receiving long-term voriconazole therapy. *Clin Infect Dis* 2011; **52**: 604-611 [PMID: 21239842 DOI: 10.1093/cid/ciq188]
12 **Wise SM**, Wilson MA. A case of periostitis secondary to voriconazole therapy in a heart transplant recipient. *Clin Nucl Med* 2011; **36**: 242-244 [PMID: 21285691 DOI: 10.1097/RLU.0b013e31820902d8]
13 **Becce F**, Malghem J, Lecouvet FE, Vande Berg BC, Omoumi P. Clinical images: voriconazole-induced periostitis deformans. *Arthritis Rheum* 2012; **64**: 3490 [PMID: 22777747 DOI: 10.1002/art.34618]
14 **Demrouelle K**. Voriconazole-induced nodular hypertrophic osteoarthropathy. 2012. [cited 7 April 2021]. Available from: http://www.rheumatologywinterclinicalsymposium.com/webposters2012/01_Demoruelle/
15 **Gerber B**, Guggenberger R, Fasler D, Nair G, Manz MG, Stussi G, Schanz U. Reversible skeletal disease and high fluoride serum levels in hematologic patients receiving voriconazole. *Blood* 2012; **120**: 2390-2394 [PMID: 22859610 DOI: 10.1182/blood-2012-01-403030]
16 **Pampaloni MH**. Voriconazole-Associated Periostitis in a Heart Transplant Patient. *J Clin Case Rep* 2012; **2**: 166 [DOI: 10.4172/2165-7920.1000166]
17 **Rossier C**, Dunet V, Tissot F, Aubry-Rozier B, Marchetti O, Boubaker A. Voriconazole-induced periostitis. *Eur J Nucl Med Mol Imaging* 2012; **39**: 375-376 [PMID: 21894545 DOI: 10.1007/s00259-011-1922-x]
18 **Bucknor MD**, Gross AJ, Link TM. Voriconazole-induced periostitis in two post-transplant patients. *J Radiol Case Rep* 2013; **7**: 10-17 [PMID: 24421948 DOI: 10.3941/jrcr.v7i8.1458]
19 **Gladue HS**, Fox DA. Voriconazole-induced periostitis causing arthralgias mimicking a flare of granulomatosis with polyangiitis. *J Clin Rheumatol* 2013; **19**: 444-445 [PMID: 24263147 DOI: 10.1097/RHU.0000000000000045]
20 **Launay E**, Thomas C, Gras-Le Guen C, Geffroy L, Moreau A, Lortholary O. Photo quiz. Generalized pain in a 20-year-old man with chronic granulomatous disease. *Clin Infect Dis* 2013; **57**: 562-563, 616 [PMID: 23881728 DOI: 10.1093/cid/cit339]
21 **Tedja R**, El-Sherief A, Olbrych T, Gordon S. Multifocal periostitis as a complication of chronic use of voriconazole in a lung transplant recipient. *Transpl Infect Dis* 2013; **15**: 424-429 [PMID: 23663268 DOI: 10.1111/tid.12088]
22 **Hirota K**, Yasoda A, Fujii T, Inagaki N. Voriconazole-induced periostitis in a patient with overlap syndromes. *BMJ Case Rep* 2014; **2014** [PMID: 24599432 DOI: 10.1136/bcr-2013-203485]
23 **Moon WJ**, Scheller EL, Suneja A, Livermore JA, Malani AN, Moudgal V, Kerr LE, Ferguson E, Vandenberg DM. Plasma fluoride level as a predictor of voriconazole-induced periostitis in patients with skeletal pain. *Clin Infect Dis* 2014; **59**: 1237-1245 [PMID: 24992954 DOI: 10.1093/cid/ciu513]
24 **Newton KM**, Brown AW, Raya R, Gaudinski M. Voriconazole induced periostitis: "Rheumatoid arthritis" in a lung transplant patient. *AM J Resp Crit Care* 2014; **189**: A1588
25 **Raghavan M**, Hayes A. Voriconazole-associated soft tissue ossification: an undescribed cause of glenohumeral joint capsulitis. *Skeletal Radiol* 2014; **43**: 1301-1305 [PMID: 24699891 DOI: 10.1007/s00256-014-1865-y]
26 **Rankin W**, Saleem M, Grant S, Florkowski C, Coates P. Periostitis deformans secondary to

prolonged voriconazole treatment: A case study. *Pathology* 2014; **46**: S86-S86 [DOI: 10.1097/01.PAT.0000443634.45947.53]

27 **Skaug M**, Spak C, Oza U. Painful periostitis in the setting of chronic voriconazole therapy. *Proc (Bayl Univ Med Cent)* 2014; **27**: 350-352 [PMID: 25484509 DOI: 10.1080/08998280.2014.11929156]

28 **Baird JH**, Birnbaum BK, Porter DL, Frey NV. Voriconazole-induced periostitis after allogeneic stem cell transplantation. *Am J Hematol* 2015; **90**: 574-575 [PMID: 25683739 DOI: 10.1002/ajh.23977]

29 **Cornejo P**. Periostitis secondary to prolonged voriconazole therapy in a child with lung transplantation for cystic fibrosis. *Pediatr Radiol* 2015; **45** Suppl 1: S155-S156 [PMID: 25861758 DOI: 10.1007/s00247-015-3297-9]

30 **Davis DL**. Voriconazole-related periostitis presenting on magnetic resonance imaging. *Clin Cases Miner Bone Metab* 2015; **12**: 78-81 [PMID: 26136804 DOI: 10.11138/ccmbm/2015.12.1.078]

31 **Glushko T**, Colmegna I. Voriconazole-induced periostitis. *CMAJ* 2015; **187**: 1075 [PMID: 26032311 DOI: 10.1503/cmaj.141025]

32 **Patel MS**, Wright AJ, Kohn R, Markmann JF, Kotton CN, Vagefi PA. Successful long-term management of invasive cerebral fungal infection following liver transplantation. *Mycoses* 2015; **58**: 181-186 [PMID: 25590987 DOI: 10.1111/myc.12289]

33 **Paudyal S**, Dummer S, Battu P, Taylor S, Sharma S, Carbone L. Fluffy Periostitis Induced by Voriconazole. *Arthritis Rheumatol* 2015; **67**: 3297 [PMID: 26246048 DOI: 10.1002/art.39314]

34 **Rad B**, Saleem M, Grant S, Florkowski C, Coates P, Gordon D, Rankin W. Fluorosis and periostitis deformans as complications of prolonged voriconazole treatment. *Ann Clin Biochem* 2015; **52**: 611-614 [PMID: 25587196 DOI: 10.1177/0004563214568873]

35 **Rheinboldt M**, Delproposto Z, Agarwal R. Voriconazole-induced periostitis post transplant: an illustrative review of thoracic computed tomography imaging manifestations. *Transpl Infect Dis* 2015; **17**: 859-863 [PMID: 26346289 DOI: 10.1111/tid]

36 **Tailor TD**, Richardson ML. Case 215: voriconazole-induced periostitis. *Radiology* 2015; **274**: 930-935 [PMID: 25710343 DOI: 10.1148/radiol.14122800]

37 **Tarlock K**, Johnson D, Cornell C, Parnell S, Meshinchi S, Baker KS, Englund JA. Elevated fluoride levels and periostitis in pediatric hematopoietic stem cell transplant recipients receiving long-term voriconazole. *Pediatr Blood Cancer* 2015; **62**: 918-920 [PMID: 25327935 DOI: 10.1002/pbc.25283]

38 **Reber JD**, McKenzie GA, Broski SM. Voriconazole-induced periostitis: beyond post-transplant patients. *Skeletal Radiol* 2016; **45**: 839-842 [PMID: 26980228 DOI: 10.1007/s00256-016-2365-z]

39 **Sircar M**, Kotton C, Wojciechowski D, Safa K, Gilligan H, Heher E, Williams W, Thadhani R, Tolkoff-Rubin N. Voriconazole-Induced Periostitis & Enthesopathy in Solid Organ Transplant Patients: Case Reports. *J Biosci Med (Irvine)* 2016; **4**: 8-17 [PMID: 27990445 DOI: 10.4236/jbm.2016.411002]

40 **Sweiss K**, Oh A, Rondelli D, Patel P. Voriconazole-Induced Periostitis Mimicking Chronic Graft-versus-Host Disease after Allogeneic Stem Cell Transplantation. *Case Rep Infect Dis* 2016; **2016**: 3242196 [PMID: 27403356 DOI: 10.1155/2016/3242196]

41 **Thekkudan SF**, Kumar P, Nityanand S. Voriconazole-induced skeletal fluorosis in an allogenic hematopoietic stem cell transplant recipient. *Ann Hematol* 2016; **95**: 669-670 [PMID: 26820975 DOI: 10.1007/s00277-016-2603-4]

42 **Cormican S**, Adams N, O'Connell P, McErlean A, de Freitas D. Voriconazole-induced periostitis deformans: serial imaging in a patient with ANCA vasculitis. *Skeletal Radiol* 2018; **47**: 191-194 [PMID: 28866833 DOI: 10.1007/s00256-017-2764-9]

43 **Ladak K**, Rubin L. Voriconazole-Induced Periostitis Deformans: A Mimicker of Hypertrophic Pulmonary Osteoarthropathy. *Clin Med Res* 2017; **15**: 19-20 [PMID: 28487449 DOI: 10.3121/cmr.2017.1357]

44 **Metayer B**, Bode-Milin C, Ansquer C, Haloun A, Maugars Y, Berthelot JM. Painful and swollen hands 3 months after lungs graft: Suracute voriconazole-induced periostitis and exostosis. *Joint Bone Spine* 2017; **84**: 97-98 [PMID: 27117297 DOI: 10.1016/j.jbspin.2015.11.011]

45 **Hussain S**. Voriconazole-induced Severe Periostitis Deformans. *J Coll Physicians Surg Pak* 2018; **28**: S114-S116 [PMID: 29866241 DOI: 10.29271/jcpsp.2018.06.S114]

46 **Gayán Belmonte MJ**, Botía González CM, García Gerónimo A, Martínez Fernández M, González Moreno IM. Voriconazole-Induced Periostitis: Radiological Clues for its Diagnosis. *J Clin Rheumatol* 2019; **25**: e67 [PMID: 29319553 DOI: 10.1097/RHU.0000000000000646]

47 **Poinen K**, Leung M, Wright AJ, Landsberg D. A vexing case of bone pain in a renal transplant recipient: Voriconazole-induced periostitis. *Transpl Infect Dis* 2018; **20**: e12941 [PMID: 29873153 DOI: 10.1111/tid.12941]

48 **Elmore S**, Wisse A, Chapin RW, Whelan TP, Silver RM. Voriconazole-associated periostitis presenting as hypertrophic osteoarthropathy following lung transplantation report of two cases and review of the literature. *Semin Arthritis Rheum* 2019; **49**: 319-323 [PMID: 31103239 DOI: 10.1016/j.semarthrit.2019.04.003]

49 **Haemels M**, Pans S, Schoemans H, Goffin K, Gheysens O, Jentjens S. Voriconazole-Induced Periostitis After Allogeneic Stem Cell Transplantation. *Clin Nucl Med* 2019; **44**: 159-160 [PMID: 30516686 DOI: 10.1097/RLU.0000000000002383]

50 **Hedrick J**, Droz N. Voriconazole-Induced Periostitis. *N Engl J Med* 2019; **381**: e30 [PMID: 31597023 DOI: 10.1056/NEJMicm1814565]

51 **Jakobsen DM**, Justad BA, Helweg-Larsen J, Katzenstein TL. [Voriconazole-induced periostitis].

Ugeskr Laeger 2019; **181** [PMID: 31036146]
52 **Khawar T**, Hamann CR, Haghshenas A, Blackburn A, Torralba KD. A 31-Year-Old Man With A Fungal Infection, Elevated Alkaline Phosphatase Level, and Polyarthritis. *Arthritis Care Res (Hoboken)* 2020; **72**: 601-606 [PMID: 30452124 DOI: 10.1002/acr.23812]
53 **Malek AE**, Skaff Y, Mulanovich VE. Voriconazole-induced periostitis in stem cell transplant patient. *Infection* 2020; **48**: 809-810 [PMID: 32430648 DOI: 10.1007/s15010-020-01445-0]
54 **Buzalaf CP**, Leite ADL, Buzalaf MAR. Fluoride Metabolism. Fluorine: Chemistry, Analysis, Function and Effects. London: Royal Society of Chemistry, 2015: 54-72.
55 **Bratthall D**, Hänsel-Petersson G, Sundberg H. Reasons for the caries decline: what do the experts believe? *Eur J Oral Sci* 1996; **104**: 416-422; discussion 423-425, 430-432 [PMID: 8930592 DOI: 10.1111/j.1600-0722.1996.tb00104.x]
56 **Kobayashi CA**, Leite AL, Peres-Buzalaf C, Carvalho JG, Whitford GM, Everett ET, Siqueira WL, Buzalaf MA. Bone response to fluoride exposure is influenced by genetics. *PLoS One* 2014; **9**: e114343 [PMID: 25501567 DOI: 10.1371/journal.pone.0114343]
57 **Whitford GM**. Intake and metabolism of fluoride. *Adv Dent Res* 1994; **8**: 5-14 [PMID: 7993560 DOI: 10.1177/08959374940080011001]
58 **Villa A**, Anabalon M, Zohouri V, Maguire A, Franco AM, Rugg-Gunn A. Relationships between fluoride intake, urinary fluoride excretion and fluoride retention in children and adults: an analysis of available data. *Caries Res* 2010; **44**: 60-68 [PMID: 20130402 DOI: 10.1159/000279325]
59 **Zonios D**, Yamazaki H, Murayama N, Natarajan V, Palmore T, Childs R, Skinner J, Bennett JE. Voriconazole metabolism, toxicity, and the effect of cytochrome P450 2C19 genotype. *J Infect Dis* 2014; **209**: 1941-1948 [PMID: 24403552 DOI: 10.1093/infdis/jiu017]
60 the Centers for Disease Control. Public Health Service report on fluoride benefits and risks. *JAMA* 1991; **266**: 1061-1062, 1066 [PMID: 1865532]
61 **Lindsay R**. Fluoride and bone--quantity *vs* quality. *N Engl J Med* 1990; **322**: 845-846 [PMID: 2308618 DOI: 10.1056/NEJM199003223221210]
62 **Khokher MA**, Dandona P. Fluoride stimulates [3H]thymidine incorporation and alkaline phosphatase production by human osteoblasts. *Metabolism* 1990; **39**: 1118-1121 [PMID: 2233270]
63 **Buzalaf MAR**, Whitford GM. Fluoride metabolism. *Monogr Oral Sci* 2011; **22**: 20-36 [PMID: 21701189 DOI: 10.1159/000325107]
64 **Allen KC**, Sanchez CJ Jr, Niece KL, Wenke JC, Akers KS. Voriconazole Enhances the Osteogenic Activity of Human Osteoblasts In Vitro through a Fluoride-Independent Mechanism. *Antimicrob Agents Chemother* 2015; **59**: 7205-7213 [PMID: 26324277 DOI: 10.1128/AAC.00872-15]
65 **Baker AW**, Maziarz EK, Arnold CJ, Johnson MD, Workman AD, Reynolds JM, Perfect JR, Alexander BD. Invasive Fungal Infection After Lung Transplantation: Epidemiology in the Setting of Antifungal Prophylaxis. *Clin Infect Dis* 2020; **70**: 30-39 [PMID: 30801642 DOI: 10.1093/cid/ciz156]
66 **Ullmann AJ**, Aguado JM, Arikan-Akdagli S, Denning DW, Groll AH, Lagrou K, Lass-Flörl C, Lewis RE, Munoz P, Verweij PE, Warris A, Ader F, Akova M, Arendrup MC, Barnes RA, Beigelman-Aubry C, Blot S, Bouza E, Brüggemann RJM, Buchheidt D, Cadranel J, Castagnola E, Chakrabarti A, Cuenca-Estrella M, Dimopoulos G, Fortun J, Gangneux JP, Garbino J, Heinz WJ, Herbrecht R, Heussel CP, Kibbler CC, Klimko N, Kullberg BJ, Lange C, Lehrnbecher T, Löffler J, Lortholary O, Maertens J, Marchetti O, Meis JF, Pagano L, Ribaud P, Richardson M, Roilides E, Ruhnke M, Sanguinetti M, Sheppard DC, Sinkó J, Skiada A, Vehreschild MJGT, Viscoli C, Cornely OA. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. *Clin Microbiol Infect* 2018; **24** Suppl 1: e1-e38 [PMID: 29544767 DOI: 10.1016/j.cmi.2018.01.002]
67 **Ashley ESD**, Lewis R, Lewis JS, Martin C, Andes D. Pharmacology of Systemic Antifungal Agents. *Clin Infect Dis* 2006; **43**: S28-S39 [DOI: 10.1086/504492]
68 **Pascual A**, Calandra T, Bolay S, Buclin T, Bille J, Marchetti O. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. *Clin Infect Dis* 2008; **46**: 201-211 [PMID: 18171251 DOI: 10.1086/524669]
69 **Thompson GR 3rd**, Bays D, Cohen SH, Pappagianis D. Fluoride excess in coccidioidomycosis patients receiving long-term antifungal therapy: an assessment of currently available triazoles. *Antimicrob Agents Chemother* 2012; **56**: 563-564 [PMID: 22005993 DOI: 10.1128/AAC.05275-11]
70 **Tan I**, Lomasney L, Stacy GS, Lazarus M, Mar WA. Spectrum of Voriconazole-Induced Periostitis With Review of the Differential Diagnosis. *AJR Am J Roentgenol* 2019; **212**: 157-165 [PMID: 30403528 DOI: 10.2214/AJR.18.19991]

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MINIREVIEWS

Journey of a patient with scleroderma from renal failure up to kidney transplantation

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Abstract

The increased awareness of systemic sclerosis (SS) and its pathogenetic background made the management of this disease more amenable than previously thought. However, scleroderma renal crisis (SRC) is a rarely seen as an associated disorder that may involve 2%-15% of SS patients. Patients presented with earlier, rapidly progressing, diffuse cutaneous SS disease, mostly in the first 3-5 years after non-Raynaud clinical manifestations, are more vulnerable to develop SRC. SRC comprises a collection of acute, mostly symptomatic rise in blood pressure, elevation in serum creatinine concentrations, oliguria and thrombotic microangiopathy in almost 50% of cases. The advent of the antihypertensive angiotensin converting enzyme inhibitors in 1980 was associated with significant improvement in SRC prognosis. In a scleroderma patient maintained on regular dialysis; every effort should be exerted to declare any possible evidence of renal recovery. A given period of almost two years has been suggested prior to proceeding in a kidney transplant (KTx). Of note, SS patients on dialysis have the highest opportunity of renal recovery and withdrawal from dialysis as compared to other causes of end-stage renal disease (ESRD). KTx that is the best well-known therapeutic option for ESRD patients can also be offered to SS patients. Compared to other primary renal diseases, SS-related ESRD was considered for a long period of

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poor patient and allograft survivals. Pulmonary involvement in an SS patient is considered a strong post-transplant independent risk factor of death. Recurrence of SRC after transplantation has been observed in some patients. However, an excellent post-transplant patient and graft outcome have been recently reported. Consequently, the absence of extrarenal manifestations in an SS-induced ESRD patient can be accepted as a robust indicator for a successful KTx.

Key Words: Systemic sclerosis; Scleroderma renal crisis; Risk factors; Renal failure; Hemodialysis; Kidney transplant

Core Tip: The current progress in the management of systemic sclerosis has its impact on improving patient's survival and quality of life. Patients developed scleroderma renal crisis have greatly managed after commencing angiotensin converting enzyme inhibitors. Moreover, scleroderma patient with kidney failure has a marvelous therapeutic option receiving a kidney transplant with a greatly improved extrarenal manifestations. However, patients with end stage kidney failure, maintained on regular dialysis, should have enough period permitting renal recovery before attempting the transplant procedures. This duration may be actually extended up to two years. Patients with scleroderma may show the highest rate of renal recovery among dialysis patients.

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INTRODUCTION

Scleroderma or systemic sclerosis (SS) is an autoimmune disorder that comprises vasculopathy, inflammatory changes, deposited collagen and fibrotic alterations involving the skin and vital organs. The involved organs are usually related to the current types of autoantibody found in SS patients. However, two types have been considered with SS cutaneous involvement: Limited cutaneous SS (lcSS) with thickened skin involving the elbow and knee joints, and the diffuse type (dcSS) with widespread skin affection. SS is primarily seen in females, with a prevalence rate of 7-489 case(s) *per* million population (PMP) and an incidence of 0.6-122 case(s) PMP/year, with geographic variability[1-3]. Systemic SS involvement can be observed as pulmonary fibrosis, pulmonary arterial hypertension (HT), gastrointestinal (GI) malfunctions, malignancies, and scleroderma renal crisis (SRC), rarely seen but quite devastating complication. Vasculopathic kidney lesions are commonly observed in SS patients and usually associated with isolated proteinuria and/or HT[4,5]. These manifestations, however, are not reliable in SRC prediction[6]. The clinical features of SRC include: (1) Oliguria/anuria; (2) Elevated SCr concentrations; and (3) A newly presented, usually symptomatizing HT [blood pressure (BP) > 140/90 mmHg or a > 30 mmHg elevation above its baseline].

Microangiopathic hemolytic anemia (MAHA) can be seen in almost half of cases that can be manifested by a proteinuria/hematuria syndrome with red blood cells fragmentations[7,8]. SRC is more commonly observed with the diffuse type of SS as compared with the limited one, particularly with the rapidly progressive dcSS in the first 3-5 years of disease onset. Predictors of SRC may include the following: (1) Anti-RNA polymerase III autoantibodies; (2) Tendon friction rub, and synovitis[9]; and (3) Steroid therapy (> 7.5 mg/d) may induce a dose-related impact on the SRC evolution risk[7,10].

Furthermore, and despite controversial, angiotensin converting enzyme inhibitors (ACEi) therapy before the sudden rise in BP and SCr level elevations may be accompanied with a higher risk of dialysis (DX) or mortality rates (MR)[7,10,11].

SCLERODERMA PATIENT WITH RENAL CRISES

Definition

The characteristic features of SRC may include: (1) New onset; (2) Moderate/severe HT; (3) Acute rise in SCr[12,13]; and/or (4) Almost half of cases may show MAHA[7,14].

On contrary to this definition, cases with an acute rise in SCr with normal BP are named the normotensive renal crises (10% of cases)[14]. With absence of a definite etiology, kidney biopsy may be warranted to settle the diagnosis and clarify the prognostic implications[12,15] (Figure 1).

Epidemiology

Incidence: Age- and sex-adjusted incidence of renal replacement therapy (RRT) for scleroderma-induced end-stage renal disease (ESRD) in the period from 2002 to 2013 approached only 0.18 PMP with insignificant decline in SS incidence by time. Scleroderma is estimated to be a rare disease with annual incidence approaching 10-20 pmp and a prevalence of 30-300 pmp[16] (Figure 2).

Prevalence

On the other hand, a significant rise in SS prevalence from 0.80 pmp in 2002 to 0.89 pmp in 2013. A higher prevalence of scleroderma in North America and Australia as compared to Europe or Asia has been observed[17,18]. In view of the improving patients' outcome and increased awareness of the nature of the disease, an increased prevalence of SS has been reported[2] this is despite the lower incidence of SRC that has been given by a more recent report[19]. A significant decline in RRT-dependent SS patients in Australia and New Zealand in the period between 2002 to 2013, from 0.51 pmp to 0.18 pmp[20]. However, Hruskova *et al*[16], observed an insignificant nominal decline in incidence of RRT-dependent SS patients[16]. The observed fluctuation in incidence has been expected considering the rarity of this disease. Between 2002 and 2013, the range of adjusted annual incidence and prevalence rates of RRT for SS-induced ESRD were 0.11-0.26 and 0.73-0.95 pmp), respectively[16] (Figure 2).

Pathophysiology: The vasculopathy-induced decline in kidney perfusion as well as the activated endothelial cell are considered the main contributors in SRC development, but the exact triggering factor of SRC evolution still uncertain. The major criteria of SRC pathology include injured endothelial cells with thick intima and a characteristic fibrotic 'onion-skin' fashion of the interlobular/arcuate renal arteries[14,21] (Figure 1). In addition, a prominently observed juxtaglomerular apparatus may invite the assumption that plasma renin could be involved in SRC pathogenesis[21]. However, renin estimation is not usually observed high and not necessarily related to the SRC aggressiveness. Other novel agents, however, are currently studied to elucidate their role in SRC evolution[8,19,22], *e.g.*, endothelin (ET)-1 may be included in SRC evolution, a higher plasma ET-1 level and a unique express of ET-A/ET-B in kidney tissues have been observed[22,23]. Furthermore, almost half of the SRC patients may express MAHA that indicate a proposed role of endothelial cell derangement in SRC evolution[24]. The lack of inflammatory infiltrates in kidney biopsy and the observed arteriolar intimal thickening, fibrinoid necrosis, and intimal cell proliferation, are all in favor of the postulation that an ischemic vascular damage may override the immune system triggering effects[21,22]. Nonetheless, autoimmunity cannot be excluded from activating the endothelial tissues. On the other hand, the robust relationship between SRC and anti-RNA polymerase (RNAP) III antibodies may shed the light on the possible role of autoimmunity in SRC evolution[25]. However, more research work-up still warranted to elucidate the role of autoantibodies in SRC development.

Predictive factors

More than 80% of SRC patients may exhibit the diffuse type of cutaneous involvement, particularly that is characterized by a rapidly progressive behavior. Previous data have recognized the predominant indicators of SRC evolution as follows: (1) Newly diagnosed anemia; (2) Cardiac involvement (*e.g.*, pericarditis and congestive heart failure); (3) Rapidly developed skin thickening; (4) Systemic inflammations: Arthralgia, synovitis, and tendon friction rub[25,26]; and (5) Dpenicillamine therapy in SS, large joint contracture (approximately 13% of SRC patients)[12,27].

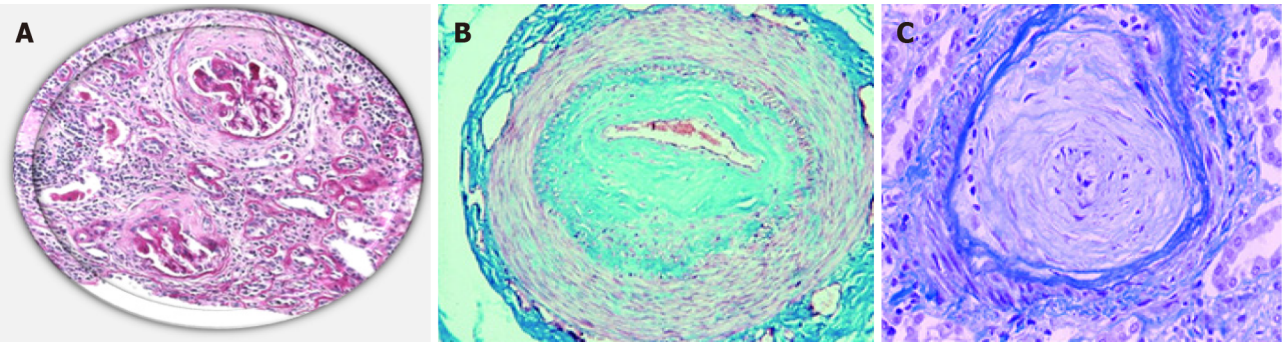

Figure 1 Pathology of scleroderma renal crisis. A: Normotensive patient with systemic sclerosis (SS) and acute renal failure. End-stage renal disease: Crescentic glomerulonephritis showing fibrous crescents. A mixed mononuclear cell infiltrate and considerable tubular loss[21,70] (Open access); B: Masson's trichrome staining of a digital artery from a patient with SS[21,70] (Open access); C: Hematoxylin and eosin staining of a renal artery from a patient with SS. Note the striking fibrotic intimal hyperplasia and the adventitial fibrosis in the digital artery and the onion skin–like intimal thickening composed of smooth muscle cells and increased connective tissue matrix in the renal artery. The intimal hyperplasia results in critical luminal narrowing and even occlusion[21,70] (Open access). Citation: Soukup T, Toms J, Oreska S, Honsova E, Safranek R. Renal Involvement in Systemic Sclerosis, 9 July 2019. Copyright© The Authors 2019. Published by Open access peer-reviewed chapter. Matucci-Cerinic M, Kahaleh B, Wigley FM. Review: evidence that systemic sclerosis is a vascular disease. *Arthritis Rheum* 2013; 65: 1953-1962. Copyright© The Authors 2013. Published by Wiley Online Library.

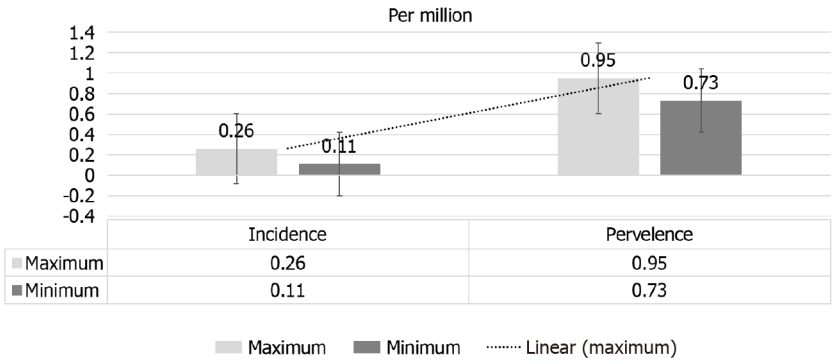

Figure 2 Range of adjusted annual incidence and prevalence rates of renal replacement therapy for end-stage renal disease due to scleroderma.

Differential diagnosis

Recognition of acute renal failure (ARF) as a sequala of SS is not always clear. About 10%-20% of SS patients could be presented with normal BP[14], moreover, SRC could be their firstly observed manifestation of SS[8]. Differential diagnosis (DD) may include: (1) Lupus Nephritis[21]; (2) Thrombotic thrombocytopenic purpura[28]; (3) Crescentic rapidly progressive glomerulonephritis (RPGN); and (4) Anti-neutrophil cytoplasmic antibody (ANCA)-related glomerulonephritis (GN).

Other DD may include membranous and membranoproliferative GN, other vasculitis *e.g.*, mixed cryoglobulinemia, and Goodpasture syndrome, drug-induced nephropathies [D-penicillamine or cyclosporin (CyA)], oxalate nephropathy, renal artery stenosis, and pre-renal causes (*e.g.*, sepsis and dehydration)[21]. All are uncommon presentations of ARF in SS that can be currently confused with SRC. DD of these disorders is currently crucial[12] (Figure 3).

Autoantibodies

Almost 90%-95% of SS patients may experience circulating antinuclear antibodies that could be detected *via* one of the following: Immunofluorescence, enzyme-linked immunosorbent assay, immunodiffusion, in addition to immunoblotting. A variety of antinuclear antibody specifically related to SS including antibodies to topoisomerase (anti-TOPO I), kinetochore proteins, RNA polymerase enzyme (anti-RNAP III), ribonuclear proteins and nucleolar antigens. Clinically, these autoantibodies specified to SS disease could be currently linked to distinct clinical criteria. So, the identification of a particular antibody could be crucial in anticipating certain organ affection that would be reflected on its timely control[29].

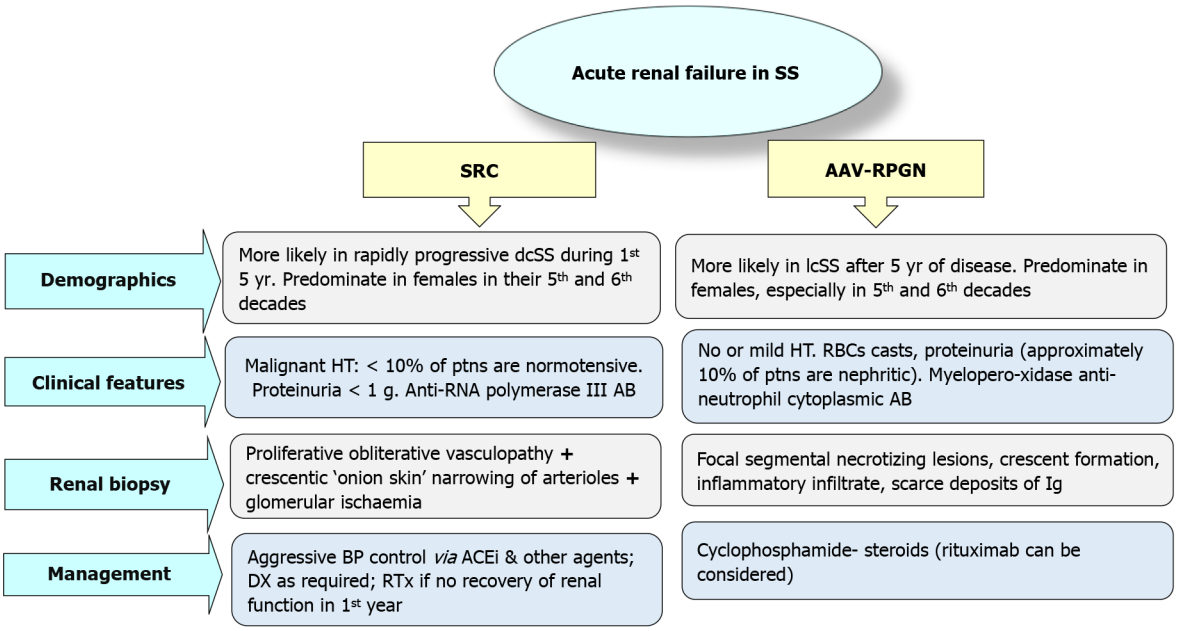

Figure 3 Differential diagnosis of acute renal failure in scleroderma: Associated vasculitis–rapidly progressive glomerulonephritis, anti-neutrophil cytoplasmic antibody-associated vasculitis with rapidly progressive glomerulonephritis. SS: Systemic sclerosis; ACE: Angiotensin converting enzyme; dcSS: Diffuse cutaneous systemic sclerosis; lcSS: Limited cutaneous systemic sclerosis; SRC: Scleroderma renal crisis; AB: Antibodies, Ig: Immunoglobulin; DX: Dialysis; RTx: Renal transplant.

Kidney biopsy

Kidney biopsy is not usually mandated for a patient presented with classic clinical criteria that include a newly presented and symptomatizing HT, elevated serum creatinine levels and a normal urine sediment. However, with a normotensive patient and raised creatinine levels with/without active urine sediment, a kidney biopsy may provide a suitable diagnostic and therapeutic guide particularly if ANCA-positive RPGN was a possibility and to exclude other comorbidities[21]. Moreover, a kidney biopsy has a prognostic implication for dialysis dependent SRC patients regarding enrolment in a kidney transplant (KTx) list. The current recommendation is to postpone KTx up to 18-24 mo after commencing DX if signs of kidney function recovery were not observed along 12 mo. A potential kidney donor should be screened for a timely provided transplant and better quality of life[12].

Prognosis

The 5-years patient's outcome in SRC has not improved after the advent of ACEi therapy[7,8,14], more plans to improve SRC outcomes are currently warranted. Pilot reports with ET receptors antagonists (ERAs) therapy have reported a reasonable safety and potential efficacy to proceed to randomized controlled trials to recognize the feasibility of ERA in limiting DX requirements and improve patient's survival[12].

How to modify the risk of SRC?

To mitigate the risk of SRC evolution, the following measures have been suggested.

BP monitoring, SCr concentrations and periodic urinalysis for patients with the following criteria: (1) Tendon friction rub[26]; (2) Large joints contracture[27]; (3) Arthralgia/synovitis[9,10,25]; (4) Steroid therapy[10,25]; (5) Early, diffuse skin involvement[30]; (6) Serum anti-RNA polymerase III AB[25,31,32]; and (7) Rapidly progressing cutaneous thickening; (modified Rodnan score more than 208).

The least dose of steroids for the minimal period allowed to manage the inflammatory manifestations[27,33] should be utilized.

Manage essential HT *via* non-ACEi regimen with calcium channel blockers (CCB) included as much as possible[33].

Start CCB for peripheral vasculopathy[33].

How to treat SRC?

It is noteworthy to mention that SRC therapeutic algorithm is currently stable for a long time. The current algorithm is simple (Figure 4), as same agents have been

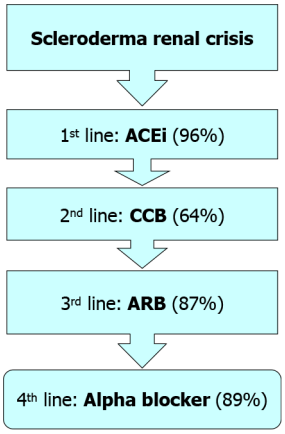

Figure 4 Algorithm for scleroderma renal crises therapy. ACE: Angiotensin-converting enzyme inhibitor; CCB: Calcium channel blockers; ARB: Angiotensin receptor blockers.

administrated to mild as well as sever cases with better experts' agreements from 66% to 81%. Since the advent of ACEi, no fundamental changes have been introduced into SRC therapeutic strategies[34]. Tight and rapid blood pressure management can be achieved *via* the addition of other antihypertensive agents. In this concept, angiotensin receptor blockers (ARBs) have been replaced by the CCBs as a second therapeutic line. Forty percent of experts would prefer keeping ACEi-despite the associated increased risk of fetal anomalies in pregnant women-if there is a history of SRC to avoid an increased risk of SRC recurrence in case of withdrawal of these agents[35].

To summarize

Renal vasculopathy *per se* cannot be considered a risk factor for SRC evolution. Owing to the growing awareness of SRC prophylactic measures, prevalence rates have been declined. Prophylactic measures against SRC development might include tight BP control in patients with early dcSS and rapid progress of skin manifestations, particularly with associated anti-RNAP III antibodies. Furthermore, the finding of active inflammation as evidenced by the presence of tendon friction rub and/or arthritis should pay patient's and his physician's attention to an increasing risk of SRC development. Given the robust association between steroid use and the evolution of SRC, this type of therapy should be limited to its lowest dosage with the possible accepted shortest period of therapy. However, the 5-years patients' survival of 50%-70% has been reported by many studies, this high percentage should be improved. Current management primarily depends on an early diagnosis, tight control of BP *via* ACEi and other agents and/or DX therapy whenever required.

For earlier SRC detection, risky patients should be asked to provide three BP readings at home at least every week, with a higher allowed level of BP > 140-150/90 mmHg. Repeat measuring after one hour, if still high, patient should contact his physician and SCr concentration should be provided with a reasonable dose of ACEi should be instituted, and patient hospitalization may be considered. However, using these agents prior to the onset of SRC may be associated with a higher risk of mortality in dcSS patients within the first 4-5 years[7,10]; ACEi therapy at this period is not currently advised. Regarding SRC in lcSS patients, safety of these agents still uncertain in view of rarity of cases and data sparsity. A retrospective study of Italian SS patients (410 with SS < 5 years), postulated that dihydropyridine CCB agents may be associated with a lower risk of SRC evolution ($P < 0.001$)[12,33].

SCLERODERMA PATIENT ON DIALYSIS

Many studies in the literature have reported poor outcome for SS patients with ESRD on dialysis[25]. For example, the French "REIN" registry, 98 SS patients dialyzed between 2001 and 2013, 81% developed ESRD secondary to SRC, while patients' survival was reported to be 75%, 55% and 32% within 1, 3- and 5-years respectively [36].

Role of ACEi and the prediction of the need to dialysis

ACEi have greatly improved SS patients' outcome[37]. One report studied 145 ACEi-treated SRC patients has showed the following: (1) 61% showed good outcome: 38%: No need for DX and 23% commenced temporary dialysis; and (2) 38% showed poor outcome: 19% was survived on DX and 19% died within 1st 6 mo[38].

A non-invasive prognostic technique is to estimate the N-terminal pro-b-type natriuretic peptide (NT-proBNP) to predict the need of DX in SRC patients. It has been shown that SRC patients requiring permanent, transient, or no DX have exhibited NT-proBNP levels of 3373 pg/mL, 1729 pg/mL, and 119 pg/mL, resp[39]. However, the role of NT-proBNP renal clearance has not been settled and well-controlled prospective studies are currently warranted to evaluate these findings. Permanent DX is usually associated with poor survival as compared to the temporary one. The prospective study (75 SRC patients) of the "International scleroderma renal crisis survey", has observed that 36% of them have died in the 1st year, whilst another 25% continued DX one year after disease onset[7]. Regarding age and disease duration, patients' survival showed inverse correlation with both patient's age and disease longevity with a survival decline from 70%-82% after one year to 50%-59% after 5 years[7,12].

Peritoneal dialysis vs hemodialysis

Whilst Hruskova *et al*[16] reported that SS patients were less vulnerable for peritoneal dialysis (PD) than hemodialysis (HD) therapy as compared to matched controls, registries coming from Australian and New Zealand reported more common use of PD in SS patients as compared to patients with other etiologies of ESRD. This finding may be explained by the more frequency of PD therapy in Europe[40]. Optimal option, however, still uncertain[16,41].

The need for RRT and outcome

The unfavorable outcome for SS patients on RRT therapy has been observed in several reports[40,42], moreover, RRT for this cohort of patients was an independent predictor of mortality[40]. Recent reports agreed with these findings particularly among diabetics[16]. Of note, cardiovascular events have been observed to be less common in SS patients as compared to diabetics that is may be limited by the high number of unknown cause of death in Hruskova *et al*[16]'s study.

Renal recovery

Data from two large studies (more than 100 SRC cases on DX) showed that kidney function has recovered in 40%-50% of cases within 8 mo in the first study, and within 11 mo in the other one. On the other hand, the Australian/New Zealand DX and Tx registries have observed that only 10% of cases have recovered a reasonable kidney function to be withdrawn from DX, and recovery was observed within the 1st 12-18 mo after commencing DX. A given explanation to the diminished recovery rates was that the cases with earlier kidney recovery (< 3 mo of DX institution) have been excluded [12] (Figure 5).

Renal recovery in this study[40] agreed with Hruskova *et al*[16] (7.6%). The latter study has reported a higher recovery rate in SS-induced ESRD patients as compared to other etiologies of ESRD (Figure 5). Of note, autoimmune disease may show a higher rate of recovery as compared to other primary renal diseases[43]. The robust possibility of kidney function recovery may support the recommended advice of postponing transplantation in these patients. This recommendation may explain the prolonged period on DX as compared to other cohorts[9]. So, patients with clear evidence of renal recovery should delay their transplant up to 18-24 mo, however, this decision may be individualized from one patient to another. On the other hand, patients with lack of any evidence of kidney function recovery after twelve months should have their opportunity to be enrolled on a transplant list[12].

Disease activity and preparation for transplantation

RRT, either HDX or PD as well as KTx are all potentially offered to SRC-induced ESRD patients. The latter option *i.e.*, KTx is known to be the best therapeutic one for this cohort of ESRD patients with the best offered outcome[44]. A thorough evaluation of the KTx recipients (KTRs) regarding stabilization of BP, various co-morbidities, and the possibility of renal recovery. The latter may necessitate basal data that can be obtained from a kidney biopsy. In addition, assessment of SRC disease activity may warrant an estimation of renin and ET-1 levels[12].

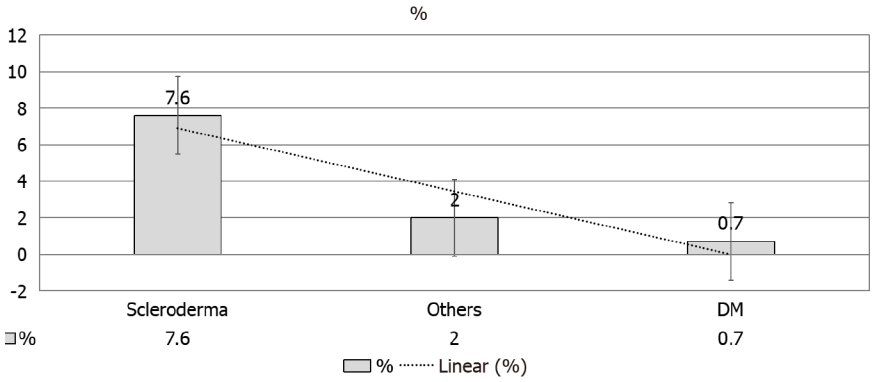

Figure 5 Recovery of independent kidney function. DM: Diabetes mellitus.

RENAL TRANSPLANTATION IN PATIENT WITH SCLERODERMA

The introduction of ACEi in SS therapy has greatly alleviated the SCR-related poor kidney and overall outcome, with an expected reversal of this serious syndrome[41,45,46]. Nevertheless, almost half of these patients still requiring long-term RRT including KTx[47]. As compared to other primary kidney diseases, old reports have observed poorer patient and allograft survival[47]. However, Bertrand *et al*[36] presented an observational study including 34 patients with SS who received KTx and uniquely reported the evolution of post-transplant extrarenal involvement[36].

Time to transplant

The proper time of renal transplantation for patients with SS requiring RRT still uncertain. SS patients are mostly experienced SRC, with about 1%-5% of them showing ANCA-associated vasculitis or MAHA[12]. Depending on the observation that 25% of patients with SRC/ESRD may recover kidney function within almost one year of DX[8,11,25,41], four articles have been published showing their experience in postponing dialysis until the point of time at which the recovery of kidney function is not certain and KTx is currently indicated[40,44,48,49].

The relative consideration of scleroderma as a highly probable disease of renal recovery, even with prolonged dialysis[50], leads to the recommendation by some experts that dialysis should be continued for at least two years before an attempt to offer a kidney to an SS patient[51]. On the other hand, Canadian guidelines admitted two conditions for offering a KTx: (1) Six months-at least-free of cytotoxic medications should be elapsed prior to any attempt of KTx; and (2) Limitation of the extrarenal manifestations[16,52].

Renal recovery, however, has been reported to be as greater as 38% in previous studies[20].

First SS transplant

Richardson[53] were firstly performed a KTx to an SS patient[53]. They were generally considering KTx a safe procedure as long as the kidney was the primary organ involved with relative stability of other lesions[36].

Immunosuppression

The role of immunosuppressive agents in KTx is crucial in improving the systemic manifestations in SS patients. However, there is no consensus in this particular setting. Ruiz *et al*[54] (1991) have postulated that CyA should be excluded from the immunosuppression regimen to avoid its vascular toxic effects, as endothelial derangement has been implicated in the pathogenesis of the SS disease. However, in Bertrand *et al*[36], study, CNI have been included in a large proportion of KTRs (91.7%) with no noticeable serious drawbacks[36]. So, a general CNI safety can be considered. In the same direction, was the glucocorticoids use in KTx, where 88.9% in this study have received high-dose steroids as an induction therapy and maintained on low-dose steroids (63.3% of patients). Steroids is classically considered a risk factor for SCR, despite the debate about their role in precipitation of SRC in KTx patients. However, steroids can be considered by many transplant clinicians a reasonable agent in the immunosuppressive protocol.

Nevertheless, owing to the relatively small number of the studied patients, an ideal protocol for immunosuppression cannot be established yet. A reasonable and commonly used regimen is the induction with antilymphocyte serum or anti- interleukin-2 receptor, and maintaining the recipient on tacrolimus, MMF and steroids. In the vast majority of patients, steroids were rapidly withdrawn. A rejection rate of 13.8% in the first year and an 8.3% SRC recurrence rate have been reported. A suggested regimen composed of mTOR inhibitors or belatacept instead of CNI has been suggested to limit CNI-induced vascular toxicity, but with no sufficient evidence[36].

Extrarenal manifestations

Gibney *et al*[44] have reported the development of skin lesions in four SS KTRs, with noticeable improvement according to the "*Rodnan score*". Considering the intensity of disease activity prior to and after KTx, this study lacks the clinico-biological data base owing to its retrospective nature[44].

However, Bertrand *et al*[36], study provides-for the 1st time-broad data base about the extrarenal manifestations during and post KTx. Despite the observed general stability of this disorder, the provided data shed the light on the importance of the cardiac and GI involvement that may getting worse after KTx (Figure 6). Accordingly, close monitoring of extrarenal manifestations would be crucial prior to and after KTx, up to the extent that stabilized extrarenal manifestations is a robust indication to proceed to KTx. This concept might be intensified by the multicenter nature of Bertrand *et al*[36], study. In addition, pulmonary involvement in an SS patient was considered as a post-transplant independent risk factor of death in this study. However, Pulmonary involvement in SS patients could be classified into two main categories: (1) Primary pulmonary affection (*i.e.*, lung parenchymal disease and pulmonary HT, PH); and (2) Secondary pulmonary involvement (*i.e.*, airway disease owing to bronco-aspiration that usually results from gastro-esophageal reflux disease, drug-induced lung toxicity and infectious causes)[55-57].

In non-transplant cohort, the associated parenchymal pulmonary disease, PH, and kidney involvement is complicated by a higher MR[58]. An associated interstitial lung disease or PH is responsible for 60% of the total MR in this cohort[57]. However, Bertrand *et al*[36] observed that in the transplant cohort, pulmonary affection appears to exert a similar impact on MR. Accordingly, a particular caution prior to KTx must be directed to explore and evaluate the presence of parenchymal pulmonary disease or PH that may preclude a KTx[36].

Allograft survival and patients' outcome in various studies

Whilst the patient survival was 100%, 90.3% and 82.5 %, the death-censored allo-graft survival was 97.2%, 97.2% and 92.8%, in one, three and five years, respectively (Figure 7) in Bertrand *et al*[36]'s study. On the other hand, the non-death-censored graft survival approached, 97.2%, 87.8% and 76.6% after 1, 3 and 5 years, resp, that was higher than that given by Gibney *et al*[44], 68.0% and 60.3% after 1 and 3 years resp, (UNOS registry: 1985-2002) (Table 1 and Figure 8). In Gibney *et al*[44], early graft loss was commonly observed during the first 90 d after transplantation and mostly related to the death with a functioning graft[44]. The following explanations have been given for the early graft loss: (1) Acute rejection; (2) Thrombotic events; and (3) SS patient, is vulnerable to early death.

In Bertrand *et al*[36] study, no early deaths with a functioning graft have been observed, and the primary non-functioning graft due to possible recurrent SRC has been reported in only one patient[36]. In Pham *et al*[59], on the other hand, the non-death-censored graft outcome at 1, 3, 5 and 10 years, resp, were 78.7%, 68.6%, 56.7% and 26.7% (UNOS: 1987-2004) that was far lower than that given by Bertrand *et al*[36]. Moreover, Bertrand *et al*[36], reported graft survival in SS patients that was far less than that observed in other primary renal disorders (79.5% and 71.8% after 1 and 3 years)[47] (Table 1 and Figure 8). Of note European and United States reports have reported poorer graft outcome as compared to that observed with other primary renal diseases[47].

In Bertrand *et al*[36], study, the death-censored graft outcome was excellent and comparable to that was reported by the global French cohort of KTx from 1993 to 2010, 91.2% after 1 year, and 79.7% after 5 years resp, (Agence de Biomédecine, annual report)[36]. They depended on the given data base that were more recent (1987-2012) as compared to that in prior literature, that may partially explain their better results. In fact, more potent immunosuppression regimen is more beneficial not only for rejection, but also for SS management, in addition to the better KTRs selection, taken together may improve graft outcome[36]. Bertrand *et al*[36], study was limited by the number of the included KTRs. Nevertheless, crucial information particularly that

Table 1 Non-death censored graft survival after one, three, five, and ten years in various studies[16,36,44,47,59]

Item	Bertrand *et al*[36], 2017	Hruskova *et al*[16], 2019	Pham *et al*[59], 2005	Gibney *et al*[44], 2004	Bleyer *et al*[47], 2001
Non-death-censored graft survival, after 1 yr	97.2%		78.7%	68.0%	79.5%
Graft survival after 3 yr	87.8%		68.6%	60.3%	71.8%
Graft survival after 5 yr	76.6%	72.4%	56.7%		
Graft survival after 10 yr			26.7%		

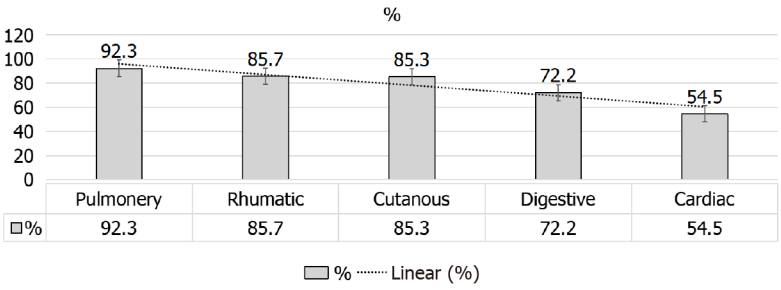

Figure 6 Stable or improved extrarenal manifestation after kidney transplantation.

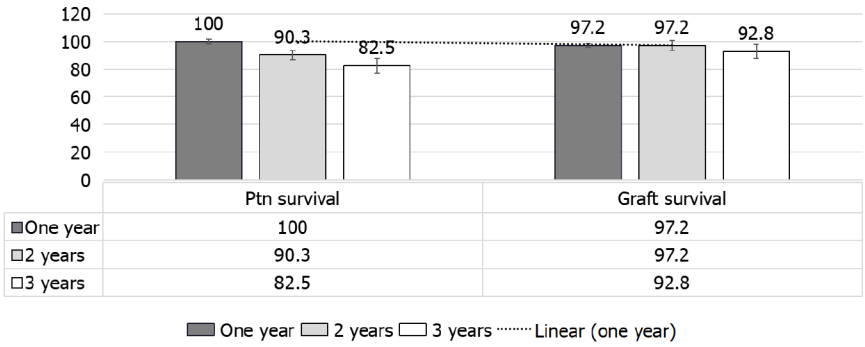

Figure 7 Patients and death-censored graft survival.

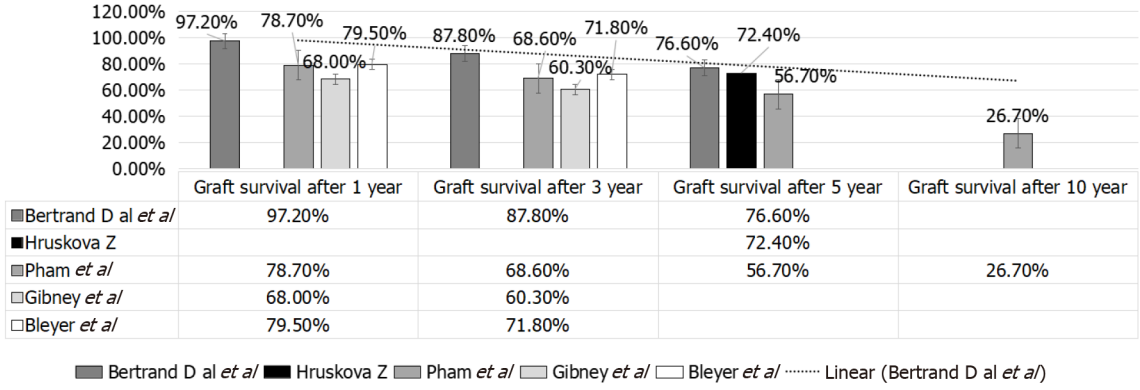

Figure 8 Graft survival after one, three, five and ten years in various studies.

related to extrarenal manifestation in SS patients and its development after KTx were lacking.

Scleroderma patients, diabetes mellitus patients, and other groups

A given comparison by Hruskova *et al*[16] (2018), for SRC patients' outcomes[16], as

compared to diabetics and patients with other primary renal disease has showed the following: (1) Less percentage of KTx for patients with SRC, 13.7% as compared to patients with diabetes mellitus, 18.7%, and those with other primary renal disease, 27.1% (both $P < 0.001$) (Figure 9); (2) Patients and allograft survival were comparable to that in other cohorts, the 5-years patient and graft survival after they receive their 1st KTx, were (88.2% and 72.4%) for SS patients and (84.3% and 76.5%) for matched control diabetics and (89.3% and 81.5%), for other primary renal diseases, respectively, matched on sex and age at KTx (Figure 10); and (3) The 5-years survival probability from day 91 of RRT in SS patients was 38.9%, as compared to the 5-years post-transplant patients' survival and allograft survival that approaches 88.2% and 72.4%, respectively[16] (Figure 11).

Post-transplant SRC recurrence

Whilst earlier case studies reported high rate of post-transplant SRC recurrence (20%-50%), more recent registries documented much less rates (1.9%-2.1%)[40,44,59]. Analysis of 260 KTx(s) in the period of 1987-2004 in SRC KTRs registered in the UNOS reported that only 1.9% of KTRs developed SRC recurrence-related graft failure between 70 and 805 days after recurrence[44]. Risk factors for SRC prediction of recurrence in the renal allograft still uncertain, many selection biases may be altering [40,44,59]. Considering the 5 well-studied cases with recurrent SRC in the literature, disease activity was associated with the following: (1) Cutaneous tightness (4 cases); (2) Anemia (2 cases); and (3) Pleuro-pericarditis and pericardial effusion (2 cases)[59].

In post-transplant SRC recurrence, less than two weeks have been elapsed from the timing of SRC development until an ESRD established. Nevertheless, an aggressive evolution of ESRD is not always associated with in SRC recurrence. However, concluding an impact of the immunosuppressive agents on SRC recurrence rates is quite difficult in view of the concerned data sparsity. In addition, the observed lower rate of recurrent SRC in the period from 1985 to 2002 (2.1%) may invite the postulation that a moderate steroid dosage (15-20 mg/d) cannot be considered an independent risk factor for SRC recurrence[12,44].

Recurrence of SRC and the reported bias

In Bertrand *et al*[36], study, 3 patients with suspected recurrent SRC (8.3%), one recurrent case was complicated by graft loss. All the recurrent cases were on CNI, steroids and ACEi. In follow up biopsies, no subclinical vascular alteration has been observed. Of note, only 6 cases with recurrent SRC have been reported in the literature. An estimated proportion of 1.9 % has been reported in the literature with recurrent SRC-induced allograft loss (UNOS database)[36].

Whilst UNOS may under-estimate the actual rate of SRC recurrence, published series may over-estimate SRC recurrence, considering the publication bias of recording serious cases with worst outcome. In addition, two potential diagnoses must be differentiated from the recurrent SCR: (1) Acute/chronic AMR; and (2) CNI toxicity[54]. Consequently, it is difficult to conclude a definite diagnosis particularly with the retrospective nature of the current reports. The SRC prediction in the non-transplant cohort is quite certain[60-63]. Recognition of RNA polymerase III could be a helpful screening technique in the setting of high-risk patients of recurrence[34,36,64].

Post-transplantation care

The finding that mTOR inhibitors may impede collagen produced from the dermal fibroblasts in vitro, may suggest a potential therapeutic role of mTORi in the cutaneous fibrotic disease[65]. In this context, Sirolimus (SRL) has been evaluated against methotrexate in early diffuse SS skin disease, an improved modified "Rodnan score" as well as the intensity of disease activity were comparable[66] but edema, HT and hypercreatinineamia were more observed SRL-treated patients.

In the same setting CyA safety has been examined in an open-label study against placebo and declared an improved skin score; UCLA skin score declined by 35% in six out of ten CyA-treated patients but still stationery in control group. Of note, transient decline in kidney function in many patients (21%) can be reversed *via* dose reduction [67]. So, an mTORi-based regimen may be suggested against CNI-based regimen for SRC KTRs candidates, however, evidence base still lacking[57]. ACEi has its crucial role as a renoprotective agent among KTRs[68]. Post-transplant SRC recurrence has been observed in KTRs who have been switched from the ACEi "captopril" to the ARB "losartan"[69], however, no sufficient evidence supporting the role of ARBs in therapy/prevention of SRC. A non-dihydropyrimide CCB agent can be administered to SS KTRs, so that CNI dosage can be reduced[12,68].

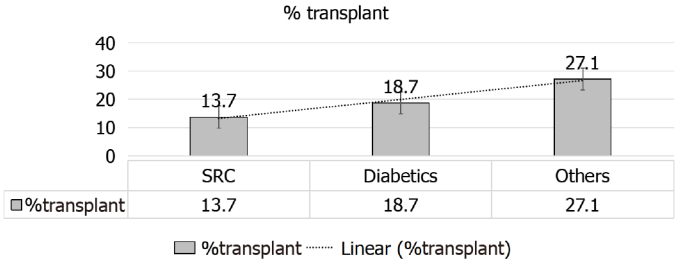

Figure 9 Percentage of scleroderma renal crisis patients received kidney allograft compared to other groups. SRC: Scleroderma renal crisis.

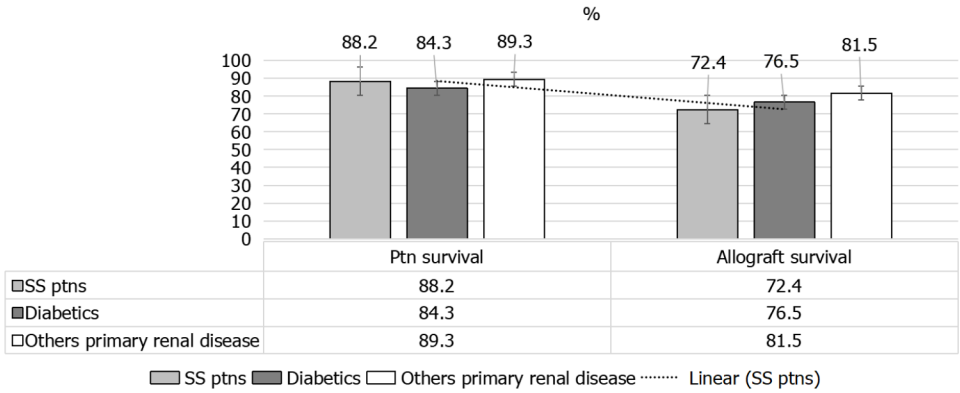

Figure 10 Patient and graft survival after receiving 1st kidney transplant, for systemic sclerosis, diabetes mellitus and other primary kidney diseases. SS: Systemic sclerosis.

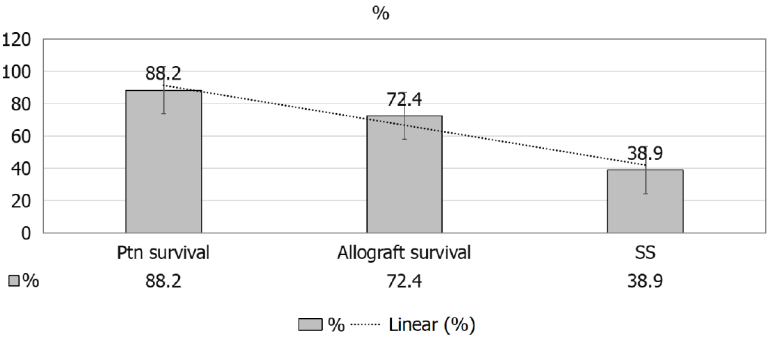

Figure 11 5-yr survival probability from day 91 of renal replacement therapy in systemic sclerosis patients, posttransplant patients' survival and 5-yr allograft survival.

CONCLUSION

SS is a multisystem disorder that can be clinically encountered in several stages. In contrary to the reported poor survival of SS patients maintained on RRT in comparison to other groups, these patients may show the highest likelihood of renal recovery permitting their withdrawal from dialysis. Recent data in the literature are in favor of better outcome of SS patients receiving a KTx as compared to the previous results. Furthermore, these results were comparable to KTRs in other groups of patients. A particular insight, however, should be focused on the extrarenal manifestations of this disease, especially those related to the pulmonary involvement, an independent risk factor of death in this cohort. Furthermore, the post-transplant cardiac and GI involvement should be closely monitored as they may getting worse. In view of the comparable patients and allograft survival rates that have been observed in transplanted SS patients with other groups, further work-up should be tailored to identify which type of an SS patient may benefit more from an offered transplant.

REFERENCES

1 **Mayes MD**, Lacey JV Jr, Beebe-Dimmer J, Gillespie BW, Cooper B, Laing TJ, Schottenfeld D. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. *Arthritis Rheum* 2003; **48**: 2246-2255 [PMID: 12905479 DOI: 10.1002/art.11073]

2 **Chifflot H**, Fautrel B, Sordet C, Chatelus E, Sibilia J. Incidence and prevalence of systemic sclerosis: a systematic literature review. *Semin Arthritis Rheum* 2008; **37**: 223-235 [PMID: 17692364 DOI: 10.1016/j.semarthrit.2007.05.003]

3 **Barnes J**, Mayes MD. Epidemiology of systemic sclerosis: incidence, prevalence, survival, risk factors, malignancy, and environmental triggers. *Curr Opin Rheumatol* 2012; **24**: 165-170 [PMID: 22269658 DOI: 10.1097/BOR.0b013e32834ff2e8]

4 **Steen VD**, Syzd A, Johnson JP, Greenberg A, Medsger TA Jr. Kidney disease other than renal crisis in patients with diffuse scleroderma. *J Rheumatol* 2005; **32**: 649-655 [PMID: 15801020]

5 **Denton CP**. Renal manifestations of systemic sclerosis--clinical features and outcome assessment. *Rheumatology (Oxford)* 2008; **47** Suppl 5: v54-v56 [PMID: 18784147 DOI: 10.1093/rheumatology/ken307]

6 **Caron M**, Hudson M, Baron M, Nessim S, Steele R; Canadian Scleroderma Research Group. Longitudinal study of renal function in systemic sclerosis. *J Rheumatol* 2012; **39**: 1829-1834 [PMID: 22859351 DOI: 10.3899/jrheum.111417]

7 **Hudson M**, Baron M, Tatibouet S, Furst DE, Khanna D; International Scleroderma Renal Crisis Study Investigators. Exposure to ACE inhibitors prior to the onset of scleroderma renal crisis-results from the International Scleroderma Renal Crisis Survey. *Semin Arthritis Rheum* 2014; **43**: 666-672 [PMID: 24176729 DOI: 10.1016/j.semarthrit.2013.09.008]

8 **Denton CP**, Lapadula G, Mouthon L, Müller-Ladner U. Renal complications and scleroderma renal crisis. *Rheumatology (Oxford)* 2009; **48** Suppl 3: iii32-iii35 [PMID: 19487221 DOI: 10.1093/rheumatology/ken483]

9 **Avouac J**, Walker UA, Hachulla E, Riemekasten G, Cuomo G, Carreira PE, Caramaschi P, Ananieva LP, Matucci-Cerinic M, Czirjak L, Denton C, Ladner UM, Allanore Y; EUSTAR collaborators*; EUSTAR collaborators. Joint and tendon involvement predict disease progression in systemic sclerosis: a EUSTAR prospective study. *Ann Rheum Dis* 2016; **75**: 103-109 [PMID: 25165035 DOI: 10.1136/annrheumdis-2014-205295]

10 **Teixeira L**, Mouthon L, Mahr A, Berezné A, Agard C, Mehrenberger M, Noël LH, Trolliet P, Frances C, Cabane J, Guillevin L; Group Français de Recherche sur le Sclérodermie (GFRS). Mortality and risk factors of scleroderma renal crisis: a French retrospective study of 50 patients. *Ann Rheum Dis* 2008; **67**: 110-116 [PMID: 17557890 DOI: 10.1136/ard.2006.066985]

11 **Woodworth TG**, Suliman YA, Li W, Furst DE, Clements P. Scleroderma renal crisis and renal involvement in systemic sclerosis. *Nat Rev Nephrol* 2016; **12**: 678-691 [PMID: 27641135 DOI: 10.1038/nrneph.2016.124]

12 **Bussone G**, Bérezné A, Pestre V, Guillevin L, Mouthon L. The scleroderma kidney: progress in risk factors, therapy, and prevention. *Curr Rheumatol Rep* 2011; **13**: 37-43 [PMID: 21061100 DOI: 10.1007/s11926-010-0145-7]

13 **Mouthon L**, Bussone G, Berezné A, Noël LH, Guillevin L. Scleroderma renal crisis. *J Rheumatol* 2014; **41**: 1040-1048 [PMID: 24833760 DOI: 10.3899/jrheum.131210]

14 **Shanmugam VK**, Steen VD. Renal manifestations in scleroderma: evidence for subclinical renal disease as a marker of vasculopathy. *Int J Rheumatol* 2010; **2010** [PMID: 20827302 DOI: 10.1155/2010/538589]

15 **Batal I**, Domsic RT, Medsger TA, Bastacky S. Scleroderma renal crisis: a pathology perspective. *Int J Rheumatol* 2010; **2010**: 543704 [PMID: 20981312 DOI: 10.1155/2010/543704]

16 **Hruskova Z**, Pippias M, Stel VS, Abad-Díez JM, Benítez Sánchez M, Caskey FJ, Collart F, De Meester J, Finne P, Heaf JG, Magaz A, Palsson R, Reisæter AV, Salama AD, Segelmark M, Traynor JP, Massy ZA, Jager KJ, Tesar V. Characteristics and Outcomes of Patients With Systemic Sclerosis (Scleroderma) Requiring Renal Replacement Therapy in Europe: Results From the ERA-EDTA Registry. *Am J Kidney Dis* 2019; **73**: 184-193 [PMID: 30122544 DOI: 10.1053/j.ajkd.2018.05.016]

17 **Ranque B**, Mouthon L. Geoepidemiology of systemic sclerosis. *Autoimmun Rev* 2010; **9**: A311-A318 [PMID: 19906362 DOI: 10.1016/j.autrev.2009.11.003]

18 **Mayes MD**. Scleroderma epidemiology. *Rheum Dis Clin North Am* 2003; **29**: 239-254 [PMID: 12841293 DOI: 10.1016/s0889-857x(03)00022-x]

19 **Shanmugam VK**, Steen VD. Renal disease in scleroderma: an update on evaluation, risk stratification, pathogenesis and management. *Curr Opin Rheumatol* 2012; **24**: 669-676 [PMID: 22955019 DOI: 10.1097/BOR.0b013e3283588dcf]

20 **ANZDATA**. Report of renal failure treatment in Australia and New Zealand from the dialysis and transplant registry (ANZDATA). *Nephrology* 1995; **1**: 105-111 [DOI: 10.1111/j.1440-1797.1995.tb00015.x]

21 **Soukup T**, Toms J, Oreska S, Honsova E, Safranek R. Renal Involvement in Systemic Sclerosis, 9 July 2019. [cited 10 January 2021]. Available from: https://www.researchgate.net/publication/334503858_Renal_Involvement_in_Systemic_Sclerosis

22 **Mouthon L**, Mehrenberger M, Teixeira L, Fakhouri F, Bérezné A, Guillevin L, Noël LH. Endothelin-1 expression in scleroderma renal crisis. *Hum Pathol* 2011; **42**: 95-102 [PMID: 20971496 DOI: 10.1016/j.humpath.2010.05.018]

23 **Penn H**, Quillinan N, Khan K, Chakravarty K, Ong VH, Burns A, Denton CP. Targeting the endothelin axis in scleroderma renal crisis: rationale and feasibility. *QJM* 2013; **106**: 839-848 [PMID: 23696678 DOI: 10.1093/qjmed/hct111]

24 **Guillevin L**, Bérezné A, Seror R, Teixeira L, Pourrat J, Mahr A, Hachulla E, Agard C, Cabane J, Vanhille P, Harle JR, Deleveaux I, Mouthon L. Scleroderma renal crisis: a retrospective multicentre study on 91 patients and 427 controls. *Rheumatology (Oxford)* 2012; **51**: 460-467 [PMID: 22087012 DOI: 10.1093/rheumatology/ker271]

25 **Sobanski V**, Dauchet L, Lefèvre G, Lambert M, Morell-Dubois S, Sy T, Hachulla E, Hatron PY, Launay D, Dubucquoi S. Prevalence of anti-RNA polymerase III antibodies in systemic sclerosis: New data from a French cohort and a systematic review and meta-analysis. *Arthritis Rheumatol* 2014; **66**: 407-417 [PMID: 24504813 DOI: 10.1002/art.38219]

26 **Doré A**, Lucas M, Ivanco D, Medsger TA Jr, Domsic RT. Significance of palpable tendon friction rubs in early diffuse cutaneous systemic sclerosis. *Arthritis Care Res (Hoboken)* 2013; **65**: 1385-1389 [PMID: 23371412 DOI: 10.1002/acr.21964]

27 **DeMarco PJ**, Weisman MH, Seibold JR, Furst DE, Wong WK, Hurwitz EL, Mayes M, White B, Wigley F, Barr W, Moreland L, Medsger TA Jr, Steen V, Martin RW, Collier D, Weinstein A, Lally E, Varga J, Weiner SR, Andrews B, Abeles M, Clements PJ. Predictors and outcomes of scleroderma renal crisis: the high-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis trial. *Arthritis Rheum* 2002; **46**: 2983-2989 [PMID: 12428241 DOI: 10.1002/art.10589]

28 **Keeler E**, Fioravanti G, Samuel B, Longo S. Scleroderma renal crisis or thrombotic thrombocytopenic purpura: seeing through the masquerade. *Lab Med* 2015; **46**: e39-e44 [PMID: 26023003 DOI: 10.1309/LM72AM5XFHZYOQCB]

29 **Stochmal A**, Czuwara J, Trojanowska M, Rudnicka L. Antinuclear Antibodies in Systemic Sclerosis: an Update. *Clin Rev Allergy Immunol* 2020; **58**: 40-51 [PMID: 30607749 DOI: 10.1007/s12016-018-8718-8]

30 **Maurer B**, Graf N, Michel BA, Müller-Ladner U, Czirják L, Denton CP, Tyndall A, Metzig C, Lanius V, Khanna D, Distler O; EUSTAR co-authors. Prediction of worsening of skin fibrosis in patients with diffuse cutaneous systemic sclerosis using the EUSTAR database. *Ann Rheum Dis* 2015; **74**: 1124-1131 [PMID: 24981642 DOI: 10.1136/annrheumdis-2014-205226]

31 **Nikpour M**, Hissaria P, Byron J, Sahhar J, Micallef M, Paspaliaris W, Roddy J, Nash P, Sturgess A, Proudman S, Stevens W. Prevalence, correlates and clinical usefulness of antibodies to RNA polymerase III in systemic sclerosis: a cross-sectional analysis of data from an Australian cohort. *Arthritis Res Ther* 2011; **13**: R211 [PMID: 22189167 DOI: 10.1186/ar3544]

32 **Hesselstrand R**, Scheja A, Wuttge DM. Scleroderma renal crisis in a Swedish systemic sclerosis cohort: survival, renal outcome, and RNA polymerase III antibodies as a risk factor. *Scand J Rheumatol* 2012; **41**: 39-43 [PMID: 22044051 DOI: 10.3109/03009742.2011.610032]

33 **Montanelli G**, Beretta L, Santaniello A, Scorza R. Effect of dihydropyridine calcium channel blockers and glucocorticoids on the prevention and development of scleroderma renal crisis in an Italian case series. *Clin Exp Rheumatol* 2013; **31**: 135-139 [PMID: 23295023]

34 **Steen VD**, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. *Ann Rheum Dis* 2007; **66**: 940-944 [PMID: 17329309 DOI: 10.1136/ard.2006.066068]

35 **Fernández-Codina A**, Walker KM, Pope JE; Scleroderma Algorithm Group. Treatment Algorithms for Systemic Sclerosis According to Experts. *Arthritis Rheumatol* 2018; **70**: 1820-1828 [PMID: 29781586 DOI: 10.1002/art.40560]

36 **Bertrand D**, Dehay J, Ott J, Sberro R, Brunelle C, Kamar N, Colosio C, Chatelet V, Albano L, Girerd S, Audard V, Barbet C, Dantal J, Ducloux D, Durrbach A, Garrigue V, Hazzan M, Heng AE, Mariat C, Merville P, Rerolle JP, Moulin B, Guerrot D. Kidney transplantation in patients with systemic sclerosis: a nationwide multicentre study. *Transpl Int* 2017; **30**: 256-265 [PMID: 28120425 DOI: 10.1111/tri.12923]

37 **Denton CP**, Black CM. Scleroderma--clinical and pathological advances. *Best Pract Res Clin Rheumatol* 2004; **18**: 271-290 [PMID: 15158741 DOI: 10.1016/j.berh.2004.03.001]

38 **Steen VD**, Medsger TA Jr. Long-term outcomes of scleroderma renal crisis. *Ann Intern Med* 2000; **133**: 600-603 [PMID: 11033587 DOI: 10.7326/0003-4819-133-8-200010170-00010]

39 **Schioppo T**, Artusi C, Ciavarella T, Ingegnoli F, Murgo A, Zeni S, Chighizola C, Meroni PL. N-TproBNP as biomarker in systemic sclerosis. *Clin Rev Allergy Immunol* 2012; **43**: 292-301 [PMID: 22669751 DOI: 10.1007/s12016-012-8312-4]

40 **Siva B**, McDonald SP, Hawley CM, Rosman JB, Brown FG, Wiggins KJ, Bannister KM, Campbell SB, Johnson DW. End-stage kidney disease due to scleroderma--outcomes in 127 consecutive ANZDATA registry cases. *Nephrol Dial Transplant* 2011; **26**: 3165-3171 [PMID: 21357212 DOI: 10.1093/ndt/gfq861]

41 **Brown N**, Summers A, Venning MC, Bruce IN. The challenges of dialysis in systemic sclerosis: between the devil and the deep blue sea? *Case Rep Nephrol* 2012; **2012**: 865193 [PMID: 24558616 DOI: 10.1155/2012/865193]

42 **Abbott KC**, Trespalacios FC, Welch PG, Agodoa LY. Scleroderma at end stage renal disease in the United States: patient characteristics and survival. *J Nephrol* 2002; **15**: 236-240 [PMID: 12113593]

43 **Hruskova Z**, Stel VS, Jayne D, Aasarød K, De Meester J, Ekstrand A, Eller K, Heaf JG, Hoitsma A, Martos Jimenéz C, Ravani P, Wanner C, Tesar V, Jager KJ. Characteristics and Outcomes of Granulomatosis With Polyangiitis (Wegener) and Microscopic Polyangiitis Requiring Renal Replacement Therapy: Results From the European Renal Association-European Dialysis and

Transplant Association Registry. *Am J Kidney Dis* 2015; **66**: 613-620 [PMID: 25975963 DOI: 10.1053/j.ajkd.2015.03.025]
44 **Gibney EM**, Parikh CR, Jani A, Fischer MJ, Collier D, Wiseman AC. Kidney transplantation for systemic sclerosis improves survival and may modulate disease activity. *Am J Transplant* 2004; **4**: 2027-2031 [PMID: 15575905 DOI: 10.1111/j.1600-6143.2004.00605.x]
45 **Steen VD**, Costantino JP, Shapiro AP, Medsger TA Jr. Outcome of renal crisis in systemic sclerosis: relation to availability of angiotensin converting enzyme (ACE) inhibitors. *Ann Intern Med* 1990; **113**: 352-357 [PMID: 2382917 DOI: 10.7326/0003-4819-113-5-352]
46 **Shor R**, Halabe A. New trends in the treatment of scleroderma renal crisis. *Nephron* 2002; **92**: 716-718 [PMID: 12372964 DOI: 10.1159/000064073]
47 **Bleyer AJ**, Donaldson LA, McIntosh M, Adams PL. Relationship between underlying renal disease and renal transplantation outcome. *Am J Kidney Dis* 2001; **37**: 1152-1161 [PMID: 11382683 DOI: 10.1053/ajkd.2001.24516]
48 **Chang YJ**, Spiera H. Renal transplantation in scleroderma. *Medicine (Baltimore)* 1999; **78**: 382-385 [PMID: 10575420 DOI: 10.1097/00005792-199911000-00003]
49 **Woodworth TG**, Furst DE. Timely renal transplantation for scleroderma end-stage kidney disease patients can improve outcomes and quality of life. *Ann Transl Med* 2019; **7**: 60 [PMID: 30906764 DOI: 10.21037/atm.2018.12.64]
50 **Chu JK**, Folkert VW. Renal function recovery in chronic dialysis patients. *Semin Dial* 2010; **23**: 606-613 [PMID: 21166875 DOI: 10.1111/j.1525-139X.2010.00769.x]
51 **Teixeira L**, Mahr A, Berezné A, Noël LH, Guillevin L, Mouthon L. Scleroderma renal crisis, still a life-threatening complication. *Ann N Y Acad Sci* 2007; **1108**: 249-258 [PMID: 17893990 DOI: 10.1196/annals.1422.027]
52 **Knoll G**, Cockfield S, Blydt-Hansen T, Baran D, Kiberd B, Landsberg D, Rush D, Cole E; Kidney Transplant Working Group of the Canadian Society of Transplantation. Canadian Society of Transplantation consensus guidelines on eligibility for kidney transplantation. *CMAJ* 2005; **173**: 1181-1184 [PMID: 16275969 DOI: 10.1503/cmaj.051291]
53 **Richardson JA**. Hemodialysis and kidney transplantation for renal failure from scleroderma. *Arthritis Rheum* 1973; **16**: 265-271 [PMID: 4577393 DOI: 10.1002/art.1780160220]
54 **Ruiz JC**, Val F, de Francisco AL, de Bonis E, Zubimendi JA, Prieto M, Canga E, Arias M. Progressive systemic sclerosis and renal transplantation: a contraindication to ciclosporin. *Nephron* 1991; **59**: 330-332 [PMID: 1956502 DOI: 10.1159/000186579]
55 **Morales-Cárdenas A**, Pérez-Madrid C, Arias L, Ojeda P, Mahecha MP, Rojas-Villarraga A, Carrillo-Bayona JA, Anaya JM. Pulmonary involvement in systemic sclerosis. *Autoimmun Rev* 2016; **15**: 1094-1108 [PMID: 27497912 DOI: 10.1016/j.autrev.2016.07.025]
56 **Desbois AC**, Cacoub P. Systemic sclerosis: An update in 2016. *Autoimmun Rev* 2016; **15**: 417-426 [PMID: 26802722 DOI: 10.1016/j.autrev.2016.01.007]
57 **Hant FN**, Herpel LB, Silver RM. Pulmonary manifestations of scleroderma and mixed connective tissue disease. *Clin Chest Med* 2010; **31**: 433-449 [PMID: 20692538 DOI: 10.1016/j.ccm.2010.05.004]
58 **Bauer PR**, Schiavo DN, Osborn TG, Levin DL, St Sauver J, Hanson AC, Schroeder DR, Ryu JH. Influence of interstitial lung disease on outcome in systemic sclerosis: a population-based historical cohort study. *Chest* 2013; **144**: 571-577 [PMID: 23450327 DOI: 10.1378/chest.12-2768]
59 **Pham PT**, Pham PC, Danovitch GM, Gritsch HA, Singer J, Wallace WD, Hayashi R, Wilkinson AH. Predictors and risk factors for recurrent scleroderma renal crisis in the kidney allograft: case report and review of the literature. *Am J Transplant* 2005; **5**: 2565-2569 [PMID: 16162209 DOI: 10.1111/j.1600-6143.2005.01035.x]
60 **Steen VD**, Medsger TA Jr, Osial TA Jr, Ziegler GL, Shapiro AP, Rodnan GP. Factors predicting development of renal involvement in progressive systemic sclerosis. *Am J Med* 1984; **76**: 779-786 [PMID: 6372452 DOI: 10.1016/0002-9343(84)90986-0]
61 **Steen VD**, Medsger TA Jr. Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. *Arthritis Rheum* 1998; **41**: 1613-1619 [PMID: 9751093 DOI: 10.1002/1529-0131(199809)41:9<1613::AID-ART11>3.0.CO;2-O]
62 **Lee AT**, Burnet S. Corticosteroid-induced scleroderma renal crisis. *Med J Aust* 2002; **177**: 459 [PMID: 12381259 DOI: 10.5694/j.1326-5377.2002.tb04893.x]
63 **Steen VD**. Scleroderma renal crisis. *Rheum Dis Clin North Am* 2003; **29**: 315-333 [PMID: 12841297 DOI: 10.1016/s0889-857x(03)00016-4]
64 **Emilie S**, Goulvestre C, Bérezné A, Pagnoux C, Guillevin L, Mouthon L. Anti-RNA polymerase III antibodies are associated with scleroderma renal crisis in a French cohort. *Scand J Rheumatol* 2011; **40**: 404-406 [PMID: 21623662 DOI: 10.3109/03009742.2011.569753]
65 **Shegogue D**, Trojanowska M. Mammalian target of rapamycin positively regulates collagen type I production *via* a phosphatidylinositol 3-kinase-independent pathway. *J Biol Chem* 2004; **279**: 23166-23175 [PMID: 15047702 DOI: 10.1074/jbc.M401238200]
66 **Su TI**, Khanna D, Furst DE, Danovitch G, Burger C, Maranian P, Clements PJ. Rapamycin versus methotrexate in early diffuse systemic sclerosis: results from a randomized, single-blind pilot study. *Arthritis Rheum* 2009; **60**: 3821-3830 [PMID: 19950289 DOI: 10.1002/art.24986]
67 **Clements PJ**, Lachenbruch PA, Sterz M, Danovitch G, Hawkins R, Ippoliti A, Paulus HE. Cyclosporine in systemic sclerosis. Results of a forty-eight-week open safety study in ten patients.

Arthritis Rheum 1993; **36**: 75-83 [PMID: 8424841 DOI: 10.1002/art.1780360113]

68 **Mangray M**, Vella JP. Hypertension after kidney transplant. *Am J Kidney Dis* 2011; **57**: 331-341 [PMID: 21251543 DOI: 10.1053/j.ajkd.2010.10.048]

69 **Cheung WY**, Gibson IW, Rush D, Jeffery J, Karpinski M. Late recurrence of scleroderma renal crisis in a renal transplant recipient despite angiotensin II blockade. *Am J Kidney Dis* 2005; **45**: 930-934 [PMID: 15861360 DOI: 10.1053/j.ajkd.2005.01.007]

70 **Matucci-Cerinic M**, Kahaleh B, Wigley FM. Review: evidence that systemic sclerosis is a vascular disease. *Arthritis Rheum* 2013; **65**: 1953-1962 [PMID: 23666787 DOI: 10.1002/art.37988]

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MINIREVIEWS

ABO incompatibility in renal transplantation

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Abstract

ABO blood group incompatibility (ABO-I) was historically considered an absolute contraindication to kidney transplantation due to the significant risk of acute antibody-mediated rejection and early graft loss. Nevertheless, the urge to minimize the gap between the candidates' number on the waitlist for kidney transplants and the available kidney donors encourage investigation into finding ways to use organs from ABO-I kidney donors, especially in the era of using more potent immunosuppression therapies. This review aims to discuss a general overview of ABO-I kidney transplantation and the different protocols adopted by some transplant centers to meaningfully overcome this barrier.

Key Words: ABO incompatibility; Renal transplantation; Kidney; Transplants

Core Tip: The urge to minimize the gap between the candidates' number on the waitlist for kidney transplants and the available kidney donors encouraged investigations into finding ways to use organs from ABO blood group incompatibility (ABO-I) kidney

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donors, especially in the era of using more potent immunosuppression therapies. In this review, we aim to discuss a general overview of ABO-I kidney transplantation and the different protocols adopted by some transplant centers to overcome this barrier.

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INTRODUCTION

Renal transplant is the most effective treatment for end-stage renal disease hence; there is an increasing demand for the organs available for transplantation[1]. The number of candidates on the waitlist for kidney transplants is more than 110000 and continues to grow every year[2].

Over the past few decades, the noted shortage in the kidney donor's pool compared to the growing number of candidates on the waitlist for kidney transplants made it necessary to loosen the kidney donors' acceptance criteria. The American Society of Transplantation validated the expanded criteria for kidney donation to include "marginal factors" such as donation from hypertensive and aged donors, those being historically declined by transplant centers[3]. The decision to accept expanded-criteria donors is still based on individual centers as the medical, legal, and ethical aspects remain uncertain[4].

Historically, ABO blood group incompatibility (ABO-I) was considered an absolute contraindication to transplantation due to the significant risk of acute antibody-mediated rejection (AAMR) and early graft loss[5]. Nevertheless, the urge to minimize the gap between the candidates' number on the waitlist for kidney transplants and the available kidney donors encourages investigation into finding ways to use organs from ABO-I kidney donors, especially in the era of using more potent immunosuppression therapies[6].

This review aims to discuss a general overview of ABO-I kidney transplantation and the different protocols adopted by some transplant centers to overcome this barrier.

BLOOD GROUP ANTIGENS AND KIDNEY TRANSPLANTATION

The blood group system is a collection of one or more antigens formed of sugar or protein present on the red blood cells' surface[7]. The ABO blood group antigens form four common categories (A, B, AB, and O). Those antigens are also expressed on lymphocytes, platelets, epithelial and endothelial cells[8]. Alloantibodies (isohemagglutinins) are naturally present and directed against the missing antigens (A and/or B) from the individual's RBCs. They appear in the blood at early infancy (four to six months of age as a function of intestinal colonization with bacteria)[9].

For decades, ABO blood group incompatibility has been considered a significant, if not absolute barrier for living kidney donation. Antibodies against A and/or B blood group antigens (either IgM or IgG) can cause antibody-mediated graft damage with worse outcomes related to preformed IgG antibodies[10]. Some studies reported worse outcomes in recipients with blood group O related to the predominant presence of anti A and B IgG antibodies (Abs) in those transplant recipients[10,11]. Egawa *et al*[12] reported a remarkable incidence of acute antibody-mediated rejection in recipients with blood group O who had ABO-I liver transplantation. Toki *et al*[5] studied the difference in acute antibody-mediated rejection (AAMR) rate and graft survival between 87 O-recipients and 77 other-than-O blood group recipients who underwent ABO-I kidney transplantation between 1990 and 2007. They reported a significantly higher rate of AAMR in blood group O recipients while there was no difference in graft survival.

ABO-I kidney transplantation was first reported by Hume *et al*[13] in 1955, where eight out of ten recipients experienced hyperacute rejection. Alexandre *et al*[14] discussed the first desensitization protocol in 1987 by undergoing splenectomy,

preoperative plasma exchange, and triple-drug immunosuppression (including azathioprine, corticosteroids, and antithymocyte globulin). They reported a 79% graft survival during the first year of kidney transplantation. The first procedure was performed in the United States in the mid-1990s while appeared in Europe with some delay by the early 2000s. An increasing success rate was reported with using kidneys from A2 blood group donors due to the low expression of A2 antigen on the cell membrane with an antibody titer of ≤ 1:8[15]. No differences in patient or graft survival were reported between the aforementioned recipients comparing those who received organs from ABO compatible (ABO-C) donors after ten years of follow-up [16]. Accepting donations from A2 and A2B donors to B recipients significantly reduce the waitlist for B recipients[17]. With the development of desensitization protocols, Tydén *et al*[18] were able to successfully perform ABO-I kidney transplantation from A1and B donors.

Desensitization techniques

The relation between the baseline antibody titer and the long-term outcome after ABO-I kidney transplantation is still unclear. Nevertheless, some studies reported a higher risk for AAMR with higher baseline antibody titers[19]. Most centers recommend maintaining the isoagglutinin titer at levels ≤ 1:16 during the first two weeks following ABO-I transplantation[20]. Different desensitization protocols were prescribed trying to allow for successful transplantation. The idea of desensitization depends on either removal of circulating ABO antibodies, immunomodulation, B cell population depletion, or combinations of those methods[21,22].

Removal of circulating ABO antibodies: Various methods have been used for decreasing ABO antibodies titer including plasmapheresis, immunoadsorption, double filtration plasmapheresis, and selective plasma exchange[23]. While the latter showed less adverse effects due to the preservation of essential plasma components, studies showed that single-use of selective plasma exchange was less efficient than unselective immunoadsorption in removing the circulating ABO antibodies[24]. Despite the effectiveness of the double filtration plasmapheresis to decreasing ABO antibodies titer, its use has been limited due to massive loss of coagulation factors which evidently increases bleeding risk[25].

Immunoadsorption is widely used in Europe. Some studies showed better graft survival rates compared to plasmapheresis. However, its use is limited by the availability and cost as the single session can cost about €3000[26]. Certain techniques are developed trying to lower the cost by using reusable columns for the same patient. However, this method is still not widely used in the United States[27]. Daily plasmapheresis, using 1.5 volume exchange with 5 percent albumin replacement with each plasmapheresis session, is the most commonly employed method in ABO-I transplantation in the United States to achieve the target titer ≤ 1:16[28]. Partial substitution with fresh frozen plasma could be used in case of abnormal coagulation profile[29].

B cell population depletion: Rituximab is a chimeric (20% rodent and 80% human) monoclonal antibody that binds to the CD20 antigen present on the cell surface and leads to depletion of mature B-cells[30,31]. It is the first approved monoclonal antibody to be used in the therapy of indolent B cell non-Hodgkin's lymphoma and chronic lymphocytic leukemia[32]. However, the role of rituximab exceeded the clinical use in cancer patients to include various immunological disorders[33]. The vital role of rituximab expanded to include the kidney transplantation field either as induction/desensitization therapy or as a treatment of antibody-associated rejection [34].

Various studies showed no significant difference regarding patient or graft survival between rituximab and splenectomy that was historically used for desensitization in ABO-I kidney transplantation[35]. The timing and dosage of rituximab are still uncertain. A Japanese study showed that B cells were completely eliminated from the circulation by using one dose of rituximab at 15, 35, 150, or 300 mg/m^2 within 3 to 13 d before transplantation. Splenic B cells were not detectable after using a single dose of 35 mg/m^2 which is the recommended dose in various centers[36].

Despite the wide use of rituximab-based protocols, the role of B cell depletion in ABO-I kidney transplantation is still unclear. Some studies showed no patient or death-censored graft survival benefits of the inclusion of rituximab[37]. Plasma cells lack CD20 receptors and are able to produce isoagglutinin antibodies that may lead to acute antibody-mediated rejection[38]. More randomized controlled studies are needed to reach a conclusion about the efficacy, dosage, and timing of rituximab-based protocol in ABO-I kidney transplantation.

Immunomodulation: While rituximab leads to B cell population depletion, IVIG can lead to suppression of T-cell differentiation and stimulation with binding to Fc receptor of the phagocytes and B cells[39]. Moreover, IVIG is able to reduce infectious complications by replenishing the loss of IgGs. A 500 mg/kg of IVIG is recommended to be used to correct the preoperative hypogammaglobulinemia induced by plasmapheresis[40].

On the other hand, administration of high-dose IVIG may lead to hemolysis as commercial IVIG may contain anti-A and anti-B isoagglutinins. Using donor blood type or AB-negative blood type plasma that contains approximately 5 grams of immunoglobulin G per unit may be considered[41].

The role of induction therapy: With intraoperative immunosuppressive management, the rate of AAMR has been dramatically decreased, allowing ABO-I renal transplantation to be considered a successful and acceptable treatment option[2]. With waiting time for deceased donor kidneys exceeding five years in certain countries, transplanting across ABO-I broadens the donor pool and reduces the burden of donor shortage [3]. With the emergence of induction therapy, ABO-I renal transplantation now accounts for one-fourth of living donor transplantations in German centers and almost one-third of procedures in Japanese centers[6].

Induction therapy is an immunosuppressive therapy administered at the time of kidney transplantation to reduce the risk of allograft rejection[42,43]. In general, induction therapy falls into one of two categories[44]. The first relies on rabbit antithymocyte globulin (ATG), which is a lymphocyte-depleting polyclonal antibody. The other more common form of induction therapy utilizes interleukin 2 receptor antagonists (IL-2 RA)[44].

Previous studies have found that ABO-I kidney transplant maintained on tacrolimus, mycophenolate mofetil, and steroids have lower acute rejection rates when using ATG induction therapy compared to using basiliximab induction therapy[6].

On the other hand, other studies suggested that IL-2 RA induction therapy involving basiliximab eliminates the need for steroid maintenance therapy while providing effective induction of immunosuppression in ABO-I kidney transplant recipients[45].

Future studies would benefit from a randomized control trial comparing patients undergoing ABO-I kidney transplantation maintained on tacrolimus and receiving ATG for induction therapy to patients undergoing ABO-I kidney transplantation maintained on tacrolimus and receiving IL-2 RA for induction therapy.

The complication of ABO-I renal transplantation

Infection: ABO-I renal transplant patients have a higher risk for infectious complications due to intensified desensitization[46]. A retrospective study for 68 recipients of living kidney with 47 ABO-C *vs* 21 ABO-I showed that ABO-I has a significantly higher infection rate and longer hospitalization than the ABO-C group. Polyomavirus (BKV), cytomegalovirus (CMV), herpes simplex virus and varicella zoster virus, are the most common viral causes[6,46]. The incidence and severity of CMV infection were greater in the ABO-I group than in the ABO-C group. CMV may cause ureteric stenosis due to urethritis[46]. Zschiedrich *et al*[47] performed a single-center retrospective study on one hundred ABO-I kidney transplants, and their study showed no significant difference between ABO-I and ABO-C groups regarding infection complication and hospitalization. A meta-analysis of ABO-I renal transplant included 1,346 patients from 27 studies which reported a significant increase in severe nonviral infection (RR: 1.44, 95%CI: 1.13-1.82). CMV infection was significantly higher in ABO-I group (RR: 1.20, 95%CI: 1.04-1.37, $P = 0.01$)[6]. Infection was the cause of death in 49% of patients who were ABO-I in 49% through the first year after the transplantation compared to 13% in patients who were ABO-C[6].

Surgical complication: The ABO-I, as compared to ABO-C renal transplant patient, has a significantly higher risk for bleeding due to loss of coagulation factor during the plasmapheresis[6,47]. Unscheduled surgical intervention was higher in the ABO-I group due to increased lymphoceles[47]. Mycophenolate mofetil utilization has a statistically significant role in developing lymphocele, which should be considered during lymphocele evaluation to avoid unnecessary surgical intervention and decrease hospital length of stay[48].

Malignancy: There is no statistically significant difference in developing malignancy between ABO-I and ABOC groups despite aggressive induction therapy[23,6,47,49].

Table 1 Literature review of studies reporting the ABO blood group incompatibility transplants, complications and outcome

	Study type	Ref.	Sample size	Desensitization/immunosuppression protocols	Complications	Success rate
1	Systemic review and meta-analysis	Scurt *et al* [37]	65063 of which 7098 undergone ABOi-rTx (ABO-incompatible renal transplantation)	Rituximab based protocols *vs* non-rituximab; splenectomy groups	Risk of bleeding; the proportion of patients with sepsis was higher after ABOi-rTx than after ABOc-rTx; no statistically significant difference was observed in the risk of UTI (D2 = 48%), CMV infection (D2 = 71%), BK polyomavirus infection (D2)	Death censored graft survival became similar to that of ABOc-rTx within the first year; compared with ABOc-rTx, ABOi-rTx was associated with significantly higher 1-yr mortality (OR: 2·17; 95%CI: 1·63-2·90), P < 0.0001
2	Single-center retrospective study	Lee *et al*[54]	56	RP group (n = 26) *vs* RO group (n = 30)	No difference in complications such as antibody-mediated rejection, biliary stricture, hepatic artery thrombosis, infection, poor graft and patient survival; biliary stricture was most common 23.1% of patients (n = 6) in the RP group; 16.7% in RO group (P = 0.990); hepatic artery thrombosis: 6.7% of patients (n = 2) in the RO group only; infection: 7.7% in RP group (n = 2) and 6.7% (n = 2) in the RO group, P = 0.791	6-, 12-, and 18-mo overall survival rates were 92.3%, 80.8% and 76.9% in the RP group and 96.6%, 85.4% and 85.4% in the RO group (P = 0.5744)
3	Systemic review and meta-analysis	Lo *et al*[55]	4810	Immunoadsorption or apheresis; splenectomy or underwent splenectomy	From 68 studies: 878 of 2672 recipients (32.9%) experienced acute, rejections; of the above 878 recipients with biopsy-proven acute rejection episodes, there were 304 (34.6%) reported cases of acute antibody-mediated rejection, 213 (24.3%) reported cases of acute cellular rejection and 400 (45.6%) cases of undifferentiated acute rejection; 46 of 83 studies with 785 recipients reported on posttransplant infective complications. CMV is the most frequently reported infection, followed by urinary tract infections, polyomavirus, and BK nephropathy	Follow up time of 28 mo (SD: 26.6); immunoadsorption or apheresis: Graft survival 94.1% (95%CI: 88.2%-98.1%) and 88% (95%CI: 82.6%-91.8%); splenectomy or underwent splenectomy: Graft survival: 94.5% (95%CI: 91.6–96.5%) and 79.7% (95%CI: 72.9% - 85.1%)
4	Single center	Tanabe *et al* [52]	67	Plasmapheresis and immunoadsorption to remove anti-AB antibodies prior to kidney transplantation; induction phase with methylprednisolone, cyclosporine, azathioprine, antilymphocyte globulin, and deoxyspergualin were used for immunosuppression; splenectomy at the time of kidney transplantation in all cases	5 dies during observation.; 3 of uncontrolled bleeding due to duodenal ulcer, malignant lymphoma, cerebral hemorrhage (one each); 10 had non-tissue invasive CMV infection	Survival: 93% at 1 yr; 91% at 8 yr; graft survival 79% at 1, 2, 3 and 4 yr, 75% at 5, 6 yr, and 73% at 7 and 8 yr
5	Retrospective cohort study	Okumi *et al* [53]	Study population: 1032; 555 LKT recipients (between	All of the patients were administered a triple immunosuppressive protocol comprising CNI, antimetabolite drugs, and MP; patients transplanted between 1989 and 1997 received cyclosporine and AZA, those transplanted	Significantly higher CMV rates and adenovirus infections were observed in the ABO-ILKT recipients	There were 32 graft losses among the patients who underwent ABO-ILKT before 2004 and 99 graft losses in the

			1989–2004), 452/555 were ABO-CLKT & 103 were ABO-ILKT; 477 LKT recipients (between 2005–2013), ABO-CLKT: 333 and ABO-ILKT: 144.; (247/1032 ABO-ILKT)	between 1998 and 2000 received TAC and AZA, and those transplanted after 2001 received TAC and MMF; after 2002, all patients received basiliximab perioperatively; splenectomies were performed at the time of transplantation between 1989 and 2004; as an alternative to splenectomy, one dose of rituximab was administered 5-7 d before transplantation	compared with the ABO-CLKT recipients before 2004. There were no differences in the frequencies between the ABO-CLKT and ABO-ILKT recipients after 2005	ABO-CLKT group; the Kaplan–Meier cumulative graft survival rates at 9 years were 68.9% and 78.1% for the ABO-ILKT and ABO-CLKT groups, respectively, a difference that was significant (log-rank test: $P = 0.026$). After 2005, the 9-yr graft survival rates were 86.9% and 92.0% for the ABO-ILKT and ABO-CLKT groups, respectively, a difference that was not significant (log-rank test: $P = 0.279$); no particular causes of graft failure predominantly affected the ABO-CLKT or ABO-ILKT groups in either era
6	Retrospective cohort study	Takahashi *et al*[56]	441 (Mean age 34)	Standard immunosuppressive therapy used: (1) Extracorpeal immunomodulation to remove serum A, anti-B antibodies before transplantation; (2) Pharmacotherapy (triple-drug regiment combining calcineurin inhibitor with a steroid and an antimetabolite) 66% received cyclosporin and 34% tacrolimus; (3) Splenectomy (433 of 441 patients except 8 who were children); and (4) Anticoagulation therapy (223 patients 51% received anticoagulation; 218 patients, 49% did not)	60 patients died; 14 patients died of pneumonia; 8 of hepatic failure; 7 of heart failure; 6 of a cerebral hemorrhage; 3 with multiorgan failure with DIC; 2 patients in each: Malignant lymphoma, gastric cancer, brain tumor, gastroduodenal ulcer, acute pancreatitis, pulmonary edema, sepsis, cerebral meningitis; 1 each: Hydrocephalus, virus-associated hemophagocytic syndrome, rupture of aorta aneurysm, hemorrhage after aortic valve replacement, ileus, and suicide	Patient survival rates were 93%, 89%, 87%, 85%, and 84% at 1, 3, 5, 7, and 9 yr, respectively; corresponding graft survival rates were 84%, 80%, 71%, 65%, and 59%
7	Prospective study	Tydén *et al* [18]	67 (mean age 34.9)	Plasmapheresis and immunoadsorption were carried out to remove the anti-AB antibodies before transplantation; induction phase: Methylprednisolone, cyclosporine, azathioprine, antilymphocyte globulin and deoxyspergualin were used for immunosuppression; local irradiation of graft of 150 rad on the 1st, 3rd and 5th day after transplantation; splenectomy at the time of transplantation	5 died during observation; 3 patients with functioning grafts died of uncontrolled bleeding due to duodenal ulcer, malignant lymphoma, and cerebral hemorrhage (one patient each); 1 patient died of ischemic colitis due to secondary amyloidosis; 1 patient of a cerebral hemorrhage after graft loss due to humoral rejection; there was no fatal infectious complication; 10 patients had a non-tissue-invasive cytomegalovirus infection	Patient survival was 93% at 1 yr and 91% at 8 yr; graft survival was 79% at 1, 2, 3, and 4 yr, 75% at 5 and 6 yr, and 73% at 7 and 8 yr; patient survival was not significantly different from that of ABO-compatible patients. Graft survival was significantly different between ABO-incompatible grafts and ABO-compatible grafts
8	Prospective observational study	Masterson *et al*[50]	Study population: 84	Standard immunosuppression without antibody removal with steroids, mycophenolate, tacrolimus, and basiliximab; mycophenolate mofetil 500 mg, BID initiated 7-14 d pretransplant; then 1000 mg, BID as tolerated or at time of transplant then taper dose of 1500 mg/day by weeks 3-6, then 1000 mg/d by week 10-12; tacrolimus 0.05 mg/kg bid 2-3 d pretransplant, followed by 9-12 ng/mL for 2 weeks, 8-10 ng/mL weeks 3-4, 5-8 ng/mL weeks 5-24, 3-7 ng/mL weeks 25-52 and 2-4 ng/mL beyond 1 yr; Basilizumab 20	One patient had recurrent urinary tract infections; BK viremia in four patients by screening with spontaneous resolution following a reduction in immunosuppression; no cases of CMV disease or other opportunistic infections	At 36 mo posttransplant, patient and graft survival was 100%; at 12 mo, median (IQR) serum creatinine and eGFR were 110.5 μmol/L 77–127 and 56.5 mL/min/1.73 m^2 (48–71), respectively; at 36 mo, there was no significant change in graft function with

				mg days 0 and 4; prophylaxis against CMV and pneumocystis jiroveci pneumonia		median creatinine 104 μmol/L (82-129), eGFR 57 mL/min/1.73 m^2, and urinary albumin/creatinine ratio 2.5 mg/mmol (0.98-4.25)
9	Retrospective	Egawa *et al* [57]	66 patients (10 mo to 55 yr old)	The basic immunosuppressive regimen consisted of tacrolimus and steroids in all groups with a target tacrolimus trough level between 10 to 15 ng/mL in the first week, 5-10 ng/mL during the first post-treatment month; methylprednisolone was administered- at different doses throughout each stage; prostaglandin E1 was infused for 7 to 14 d after transplantation; cyclophosphamide was initiated 1-week pretransplant and given daily one month after transplantation, then converted to azathioprine; splenectomy was performed in all patients aged five years and older without contraindications	Incidence of intrahepatic biliary complications and hepatic necrosis in ABO-incompatible living-related grafts (18% and 8%, respectively) was significantly (P < 0.0001) greater than in ABO-compatible and ABO-identical grafts (both 0.6% and 0%, respectively)	Antibody titer and the clinical course followed prospectively during a period of 3 to 11 yr; 5-yr patient survival was 59%, 76%, and 80% for ABO-incompatible, ABO-compatible, and ABO-identical grafts, respectively (P < 0.01); in patients < 1 yr old, > or = 1 to < 8, > or = 8 to < 16, and > or = 16 yr old, 5-yr survival was 76%, 68%, 53%, and 22%, respectively
10	Retrospective study	Kimura *et al* [58]	5549 patients (ABO matched n = 2820 and major incompatible n = 1384 and bidirectional incompatible n = 143)	Among the four groups of ABO compatibility, there were no significant differences in the gender distributions of patients and donors, the number of transplantations, performance status before transplantation, conditioning regimen, GVHD prophylaxis, administration of colony-stimulating factors	The cumulative incidences of transplant-related mortality differed significantly among the four groups P < 0.0001), with the 1-yr rates being 27.9% (AB0-matched), 35.8% (major incompatibility), 34.2% (minor incompatibility), and 30.7% (bidirectional incompatibility)	Survival rates in the group with major and minor mismatches were significantly lower than the rate in the AB0-identical group (AB0-identical 63.0%; major mismatch, 56.9%; minor mismatch, 57.1% at one year)
11	Retrospective	Kim *et al*[59]	89 adult patients	Acute GVHD prophylaxis consisted of cyclosporin A (CyA) + Methotrexate (n = 57), CYA alone (n = 20), CyA plus mycophenolate mofetil (n = 11); infection prophylaxis consisting of ciprofloxacin/metronidazole/fluconazole and acyclovir	Within the first 30 d after allogeneic PBSCT, bacteremia occurred in 10 (11.2%) patients, viral infections including cytomegalovirus in 20 (22.5%) patients, and fungal infections in 12 (13.5%) patients, although the incidence of infection was not statistically different between the different groups of transplantation; bleeding occurred in 3 cases; graft failure in 3 cases; toxic hepatitis 1 case	With a median follow-up duration of 13 mo (range, 0.5–61 mo); 3-yr overall survival estimates for the ABO-identical, major/bidirectional, and the minor group were 44.6.0 ± 9.0, 43.1 ± 11.6, and 43.8 ± 13.5%, respectively (P = 0.8652)
12	Series	Montgomery *et al*[22]	60 patients	Pre-and posttransplant PP/CMV IV immunoglobulin; quadruple, sequential immunosuppression with tacrolimus and mycophenolate mofetil. Steroids were used perioperatively. Daclizumab was used for induction; splenectomy at the time of transplant was then replaced by a single dose of anti-CD20 the night prior to transplantation	3 patient deaths in the series; all 3 patients died with functioning grafts; cause of death included West Nile encephalitis (likely acquired from FFP transfusion). metastatic liver cancer	Patient survival at 1, 3, and 5 yr was 96.3%, 96.3%, and 89.4%, respectively; using a short course of PP and low-dose IVIG with standard maintenance immunosuppression, the death-censored graft survival of 60 consecutive ABO-I kidney transplants at 1, 3, and 5 yr was 98.3%, 92.9%, and 88.7%, respectively
13	Retrospective observational	Okada *et al* [60]	412; ABO-I: n = 205	ABO-I cases treated with Rituximab (n = 131); splenectomy (n = 21)	The incidence of infection was significantly higher in the ABO incompatible treated with Rituximab group than in the ABO-incompatible treated with neither rituximab nor splenectomy group	Graft survival for ABO-I was significantly lower than that for ABO compatible renal transplantation (92.8% *vs* 97.2% after five years P = 0.0037)

					[28.2% (37/131) *vs* 9.4% (5/53), $P = 0.006$]	
14	Retrospective study	Rowley *et al* [61]	158 allogeneic hematopoietic stem cell transplants from ABO-incompatible	The majority received busulfan or TBI-based conditioning regimen. 9 patients received a variety of other myeloablative conditioning regimes; 150 patients received GVHD prophylaxis consisting of cyclosporine followed by methotrexate (CSPMTX); 2 patients received MTX alone, 1 patient received cyclosporine + methotrexate, 2 patients received CSPMTX with prednisone, 3 patients received CSP and prednisone	6 patients with suspected hemolysis due to elevated bilirubin; unable to demonstrate adverse effects from hemolysis during the first 21 d of transplantation	The study was to demonstrate the risk of hemolysis

ABOi-rTX: ABO-incompatible renal transplantation; ABOc-rTX: ABO-compatible renal transplantation; ABO-CLKT: ABO-compatible living kidney transplant; ABO-ILKT: ABO-incompatible living kidney transplant; RP: Rituximab with plasmapheresis; RO: Rituximab only without plasmapheresis; OR: Odds ratio; CMV: Cytomegalovirus; CNI: Calcineurin inhibitors; CyA: Cyclosporin; CSP: Cyclosporin A; MP: Methylprednisolone; AZA: Azathioprine; TAC: Tacrolimus; MMF: Mycophenolate mofetil; CSPMTX: Cyclosporine followed by methotrexate; GVHD: Graft versus host disease; TBI: Total body irradiation; yr: year; mo: month; FFP: Fresh frozen plasma; PP: Plasmapheresis.

Summary of literature review: There has been significant progress in desensitization protocols and optimization of ABO-I transplantation. Sufficient desensitization is possible using just rituximab, but this approach has not significantly affected patient survival. In addition, the use of immunoadsorption also appeared to be a promising preconditioning strategy as an alternative to rituximab prior to ABO-I kidney transplantation. In patients who do not undergo antibody removal prior to transplantation and use only conventional immunosuppression, it is essential to have a baseline anti-blood group antibodies (ABGAb). ABGAb titer was found to be a predictor of AbMR in ABO-I. Patients with low ABGAb titers can successfully undergo ABO-I using conventional immunosuppression alone[50]. The use of pretransplant plasmapheresis in ABO-I patients, however, was found to provide additional protection. Acute rejections, especially in kidney transplantation was found to be multifactorial. Likely due to thrombosis of the renal artery, reactive neutrophilic infiltrates and fibrin deposition at the intima, and total necrosis of the renal parenchyma[51]. The mechanism behind this was thought to occur due to the anti-A/B antibodies that would bind to renal vascular endothelial cells and activate complement, platelet aggregation, and inflammation. Starting patients on desensitization and immunosuppression protocols and in some studies, anticoagulation and prophylactic antivirals/antibiotics were found to demonstrate significant improvement in ABO-I transplantation.

ABO-I living kidney transplantation offers an excellent long-term outcome and is an acceptable treatment for end-stage renal failure[52,53]. Graft survival was almost identical over the past decade regardless of ABO-incompatibility. It has been found that the occurrence of acute rejection episodes mainly influenced the longer-term renal function in ABO-I LKT within six months and donor age (over 54 years old)[52]. Although donor age had a vital role in acute rejection, some studies have found that recipient age was also identified as a factor for outcome. As mentioned above in the chart, the studies have demonstrated, in respect to LKT with ABO-incompatibility, a substantial improvement in graft survival and decreased frequency of infectious adverse events over time. Complications, although decreasing, continue to exist, and there remains an increased risk of bleeding, infections, and organ rejection which clinicians need to be aware of as they are seen not only in ABO-I transplantation but as well as in ABOc transplantation in order to prevent further adverse effects and improve patient care. The use of preemptive antibiotics and antiviral therapy may be beneficial in these patients and close surveillance of bleeding events. Reducing the dose of immunosuppressive drugs may be beneficial, as discussed in several studies mentioned in Table 1, given the risk of infection.

CONCLUSION

ABO-I was historically considered an absolute contraindication to transplantation due to the significant risk of AAMR and early graft loss. However, the need to minimize the gap between the candidates' number on the waitlist for kidney transplants and the available kidney donors encouraged investigation into finding ways to use organs from ABO-I kidney donors, especially in the era of using more potent immunosup-

pression therapies. Desensitization protocols are used to allow ABO-I kidney transplants; these protocols include plasma exchange, B-cell depletion using rituximab, immunomodulation using IVIG. Induction of immunosuppression using ATG or IL-2 RA is required in ABO-I kidney transplants. Infections are more common with ABO-I kidney transplants compared to ABO-C kidney transplants due to more potent immunosuppression.

REFERENCES

1 **Wolfe RA**, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, Held PJ, Port FK. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999; **341**: 1725-1730 [PMID: 10580071 DOI: 10.1056/NEJM199912023412303]

2 **Saran R**, Robinson B, Abbott KC, Agodoa LY, Albertus P, Ayanian J, Balkrishnan R, Bragg-Gresham J, Cao J, Chen JL, Cope E, Dharmarajan S, Dietrich X, Eckard A, Eggers PW, Gaber C, Gillen D, Gipson D, Gu H, Hailpern SM, Hall YN, Han Y, He K, Hebert H, Helmuth M, Herman W, Heung M, Hutton D, Jacobsen SJ, Ji N, Jin Y, Kalantar-Zadeh K, Kapke A, Katz R, Kovesdy CP, Kurtz V, Lavalee D, Li Y, Lu Y, McCullough K, Molnar MZ, Montez-Rath M, Morgenstern H, Mu Q, Mukhopadhyay P, Nallamothu B, Nguyen DV, Norris KC, O'Hare AM, Obi Y, Pearson J, Pisoni R, Plattner B, Port FK, Potukuchi P, Rao P, Ratkowiak K, Ravel V, Ray D, Rhee CM, Schaubel DE, Selewski DT, Shaw S, Shi J, Shieu M, Sim JJ, Song P, Soohoo M, Steffick D, Streja E, Tamura MK, Tentori F, Tilea A, Tong L, Turf M, Wang D, Wang M, Woodside K, Wyncott A, Xin X, Zang W, Zepel L, Zhang S, Zho H, Hirth RA, Shahinian V. US Renal Data System 2016 Annual Data Report: Epidemiology of Kidney Disease in the United States. *Am J Kidney Dis* 2017; **69**: A7-A8 [PMID: 28236831 DOI: 10.1053/j.ajkd.2016.12.004]

3 **Port FK**, Bragg-Gresham JL, Metzger RA, Dykstra DM, Gillespie BW, Young EW, Delmonico FL, Wynn JJ, Merion RM, Wolfe RA, Held PJ. Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors. *Transplantation* 2002; **74**: 1281-1286 [PMID: 12451266 DOI: 10.1097/00007890-200211150-00014]

4 **Gopalakrishnan G**, Gourabathini SP. Marginal kidney donor. *Indian J Urol* 2007; **23**: 286-293 [PMID: 19718332 DOI: 10.4103/0970-1591.33726]

5 **Toki D**, Ishida H, Horita S, Yamaguchi Y, Tanabe K. Blood group O recipients associated with early graft deterioration in living ABO-incompatible kidney transplantation. *Transplantation* 2009; **88**: 1186-1193 [PMID: 19935372 DOI: 10.1097/TP.0b013e3181ba07ec]

6 **de Weerd AE**, Betjes MGH. ABO-Incompatible Kidney Transplant Outcomes. *Clin J Am Soc Nephrol* 2018; **13**: 1234-1243 [PMID: 30012630 DOI: 10.2215/CJN.00540118]

7 **Daniels G**, Reid ME. Blood groups: the past 50 years. *Transfusion* 2010; **50**: 281-289 [PMID: 19906040 DOI: 10.1111/j.1537-2995.2009.02456.x]

8 **Denomme GA**. The structure and function of the molecules that carry human red blood cell and platelet antigens. *Transfus Med Rev* 2004; **18**: 203-231 [PMID: 15248170 DOI: 10.1016/j.tmrv.2004.03.006]

9 **Daniel-Johnson J**, Leitman S, Klein H, Alter H, Lee-Stroka A, Scheinberg P, Pantin J, Quillen K. Probiotic-associated high-titer anti-B in a group A platelet donor as a cause of severe hemolytic transfusion reactions. *Transfusion* 2009; **49**: 1845-1849 [PMID: 19453987 DOI: 10.1111/j.1537-2995.2009.02208.x]

10 **Shimmura H**, Tanabe K, Ishikawa N, Tokumoto T, Takahashi K, Toma H. Role of anti-A/B antibody titers in results of ABO-incompatible kidney transplantation. *Transplantation* 2000; **70**: 1331-1335 [PMID: 11087148 DOI: 10.1097/00007890-200011150-00011]

11 **Stussi G**, Huggel K, Lutz HU, Schanz U, Rieben R, Seebach JD. Isotype-specific detection of ABO blood group antibodies using a novel flow cytometric method. *Br J Haematol* 2005; **130**: 954-963 [PMID: 16156865 DOI: 10.1111/j.1365-2141.2005.05705.x]

12 **Egawa H**, Teramukai S, Haga H, Tanabe M, Fukushima M, Shimazu M. Present status of ABO-incompatible living donor liver transplantation in Japan. *Hepatology* 2008; **47**: 143-152 [PMID: 17929298 DOI: 10.1002/hep.21928]

13 **HUME DM**, MERRILL JP, MILLER BF, THORN GW. Experiences with renal homotransplantation in the human: report of nine cases. *J Clin Invest* 1955; **34**: 327-382 [PMID: 13233354 DOI: 10.1172/JCI103085]

14 **Alexandre GP**, Squifflet JP, De Bruyère M, Latinne D, Reding R, Gianello P, Carlier M, Pirson Y. Present experiences in a series of 26 ABO-incompatible living donor renal allografts. *Transplant Proc* 1987; **19**: 4538-4542 [PMID: 3321614]

15 **Breimer ME**, Brynger H, Le Pendu J, Oriol R, Rydberg L, Samuelsson BE, Vinas J. Blood group ABO-incompatible kidney transplantation biochemical and immunochemical studies of blood group A glycolipid antigens in human kidney and characterization of the antibody response (antigen specificity and antibody class) in O recipients receiving A2 grafts. *Transplant Proc* 1987; **19**: 226-230 [PMID: 3547818]

16 **Nelson PW**, Landreneau MD, Luger AM, Pierce GE, Ross G, Shield CF 3rd, Warady BA, Aeder MI, Helling TS, Hughes TM, Beck ML, Harrell KM, Bryan CF. Ten-year experience in transplantation of

A2 kidneys into B and O recipients. *Transplantation* 1998; **65**: 256-260 [PMID: 9458025 DOI: 10.1097/00007890-199801270-00020]

17 **Forbes RC**, Feurer ID, Shaffer D. A2 incompatible kidney transplantation does not adversely affect graft or patient survival. *Clin Transplant* 2016; **30**: 589-597 [PMID: 26913566 DOI: 10.1111/ctr.12724]

18 **Tydén G**, Kumlien G, Genberg H, Sandberg J, Lundgren T, Fehrman I. ABO incompatible kidney transplantations without splenectomy, using antigen-specific immunoadsorption and rituximab. *Am J Transplant* 2005; **5**: 145-148 [PMID: 15636623 DOI: 10.1111/j.1600-6143.2004.00653.x]

19 **Tobian AA**, Shirey RS, Montgomery RA, Cai W, Haas M, Ness PM, King KE. ABO antibody titer and risk of antibody-mediated rejection in ABO-incompatible renal transplantation. *Am J Transplant* 2010; **10**: 1247-1253 [PMID: 20420632 DOI: 10.1111/j.1600-6143.2010.03103.x]

20 **Toki D**, Ishida H, Setoguchi K, Shimizu T, Omoto K, Shirakawa H, Iida S, Horita S, Furusawa M, Ishizuka T, Yamaguchi Y, Tanabe K. Acute antibody-mediated rejection in living ABO-incompatible kidney transplantation: long-term impact and risk factors. *Am J Transplant* 2009; **9**: 567-577 [PMID: 19260836 DOI: 10.1111/j.1600-6143.2008.02538.x]

21 **Segev DL**, Simpkins CE, Warren DS, King KE, Shirey RS, Maley WR, Melancon JK, Cooper M, Kozlowski T, Montgomery RA. ABO incompatible high-titer renal transplantation without splenectomy or anti-CD20 treatment. *Am J Transplant* 2005; **5**: 2570-2575 [PMID: 16162210 DOI: 10.1111/j.1600-6143.2005.01031.x]

22 **Montgomery RA**, Locke JE, King KE, Segev DL, Warren DS, Kraus ES, Cooper M, Simpkins CE, Singer AL, Stewart ZA, Melancon JK, Ratner L, Zachary AA, Haas M. ABO incompatible renal transplantation: a paradigm ready for broad implementation. *Transplantation* 2009; **87**: 1246-1255 [PMID: 19384174 DOI: 10.1097/TP.0b013e31819f2024]

23 **Cen M**, Wang R, Kong W, Deng H, Lei W, Chen J. ABO-incompatible living kidney transplantation. *Clin Transplant* 2020; **34**: e14050 [PMID: 32713064 DOI: 10.1111/ctr.14050]

24 **Wahrmann M**, Schiemann M, Marinova L, Körmöczi GF, Derfler K, Fehr T, Stussi G, Böhmig GA. Anti-A/B antibody depletion by semiselective versus ABO blood group-specific immunoadsorption. *Nephrol Dial Transplant* 2012; **27**: 2122-2129 [PMID: 22086972 DOI: 10.1093/ndt/gfr610]

25 **Tobian AA**, Shirey RS, Montgomery RA, Tisch DJ, Ness PM, King KE. Therapeutic plasma exchange reduces ABO titers to permit ABO-incompatible renal transplantation. *Transfusion* 2009; **49**: 1248-1254 [PMID: 19210321 DOI: 10.1111/j.1537-2995.2008.02085.x]

26 **Biglarnia AR**, Nilsson B, Nilsson Ekdahl K, Tufveson G, Nilsson T, Larsson E, Wadström J. Desensitization with antigen-specific immunoadsorption interferes with complement in ABO-incompatible kidney transplantation. *Transplantation* 2012; **93**: 87-92 [PMID: 22113493 DOI: 10.1097/TP.0b013e31823bb689]

27 **Rostaing L**, Allal A, Del Bello A, Sallusto F, Esposito L, Doumerc N, Debiol B, Delas A, Game X, Kamar N. Treatment of large plasma volumes using specific immunoadsorption to desensitize ABO-incompatible kidney-transplant candidates. *J Nephropathol* 2016; **5**: 90-97 [PMID: 27540536 DOI: 10.15171/jnp.2016.17]

28 **Chung BH**, Lim JU, Kim Y, Kim JI, Moon IS, Choi BS, Park CW, Kim YS, Yang CW. Impact of the baseline anti-A/B antibody titer on the clinical outcome in ABO-incompatible kidney transplantation. *Nephron Clin Pract* 2013; **124**: 79-88 [PMID: 24157458 DOI: 10.1159/000355855]

29 **Keith DS**. Therapeutic apheresis in renal transplantation; current practices. *J Clin Apher* 2014; **29**: 206-210 [PMID: 24863952 DOI: 10.1002/jca.21330]

30 **Smith MR**. Rituximab (monoclonal anti-CD20 antibody): mechanisms of action and resistance. *Oncogene* 2003; **22**: 7359-7368 [PMID: 14576843 DOI: 10.1038/sj.onc.1206939]

31 **Pescovitz MD**. Rituximab, an anti-cd20 monoclonal antibody: history and mechanism of action. *Am J Transplant* 2006; **6**: 859-866 [PMID: 16611321 DOI: 10.1111/j.1600-6143.2006.01288.x]

32 **Bryan J**, Borthakur G. Role of rituximab in first-line treatment of chronic lymphocytic leukemia. *Ther Clin Risk Manag* 2010; **7**: 1-11 [PMID: 21339937 DOI: 10.2147/TCRM.S5855]

33 **Sanz I**. Indications of rituximab in autoimmune diseases. *Drug Discov Today Ther Strateg* 2009; **6**: 13-19 [PMID: 20379381 DOI: 10.1016/j.ddstr.2009.10.001]

34 **Morath C**, Zeier M, Döhler B, Opelz G, Süsal C. ABO-Incompatible Kidney Transplantation. *Front Immunol* 2017; **8**: 234 [PMID: 28321223 DOI: 10.3389/fimmu.2017.00234]

35 **Macklin PS**, Morris PJ, Knight SR. A systematic review of the use of rituximab for desensitization in renal transplantation. *Transplantation* 2014; **98**: 794-805 [PMID: 25321163 DOI: 10.1097/TP.0000000000000362]

36 **Toki D**, Ishida H, Horita S, Setoguchi K, Yamaguchi Y, Tanabe K. Impact of low-dose rituximab on splenic B cells in ABO-incompatible renal transplant recipients. *Transpl Int* 2009; **22**: 447-454 [PMID: 19144092 DOI: 10.1111/j.1432-2277.2008.00821.x]

37 **Scurt FG**, Ewert L, Mertens PR, Haller H, Schmidt BMW, Chatzikyrkou C. Clinical outcomes after ABO-incompatible renal transplantation: a systematic review and meta-analysis. *Lancet* 2019; **393**: 2059-2072 [PMID: 31006573 DOI: 10.1016/S0140-6736(18)32091-9]

38 **Sawada T**, Fuchinoue S, Kawase T, Kubota K, Teraoka S. Preconditioning regimen consisting of anti-CD20 monoclonal antibody infusions, splenectomy and DFPP-enabled non-responders to undergo ABO-incompatible kidney transplantation. *Clin Transplant* 2004; **18**: 254-260 [PMID: 15142045 DOI: 10.1111/j.1399-0012.2004.00151.x]

39 **Ephrem A**, Misra N, Hassan G, Dasgupta S, Delignat S, Duong Van Huyen JP, Chamat S, Prost F, Lacroix-Desmazes S, Kavery SV, Kazatchkine MD. Immunomodulation of autoimmune and

inflammatory diseases with intravenous immunoglobulin. *Clin Exp Med* 2005; **5**: 135-140 [PMID: 16362793 DOI: 10.1007/s10238-005-0079-y]

40 **Lee D KB**, Kim J. ABO Antibody Removal of Plasmapheresis (PP) with Intravenous Immunoglobulin (IVIG) before ABO-Incompatible (ABOI) Kidney Transplantation [abstract]. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2013. Available from: https://atcmeetingabstracts.com/abstract/abo-antibody-removal-of-plasmapheresis-pp-with-intravenous-immunoglobulin-ivig-before-abo-incompatible-aboi-kidney-transplantation/ [DOI: 10.1097/00007890-201407151-01496]

41 **Staley EM**, Carruba SS, Manning M, Pham HP, Williams LA 3rd, Marques MB, Locke JE, Lorenz RG. Anti-Blood Group Antibodies in Intravenous Immunoglobulin May Complicate Interpretation of Antibody Titers in ABO-Incompatible Transplantation. *Am J Transplant* 2016; **16**: 2483-2486 [PMID: 26913485 DOI: 10.1111/ajt.13760]

42 **Brennan DC**, Daller JA, Lake KD, Cibrik D, Del Castillo D. Rabbit antithymocyte globulin versus basiliximab in renal transplantation. *N Engl J Med* 2006; **355**: 1967-1977 [PMID: 17093248 DOI: 10.1056/NEJMoa060068]

43 **Foster CE 3rd**, Weng RR, Piper M, Laugenou K, Ichii H, Lakey J, Malinoski D. Induction therapy by anti-thymocyte globulin (rabbit) versus basiliximab in deceased donor renal transplants and the effect on delayed graft function and outcomes. *Transplant Proc* 2012; **44**: 164-166 [PMID: 22310605 DOI: 10.1016/j.transproceed.2011.12.055]

44 **Ali H**, Soliman KM, Shaheen I, Kim JJ, Kossi ME, Sharma A, Pararajasingam R, Halawa A. Rabbit anti-thymocyte globulin (rATG) vs IL-2 receptor antagonist induction therapies in tacrolimus-based immunosuppression era: a meta-analysis. *Int Urol Nephrolog* 2020; **52**: 791-802 [PMID: 32170593 DOI: 10.1007/s11255-020-02418-w]

45 **Ando T**, Tojimbara T, Sato S, Nakamura M, Kawase T, Kai K, Nakajima I, Fuchinoue S, Teraoka S. Efficacy of basiliximab induction therapy in ABO-incompatible kidney transplantation: a rapid steroid withdrawal protocol. *Transplant Proc* 2004; **36**: 2182-2183 [PMID: 15518793 DOI: 10.1016/j.transproceed.2004.07.051]

46 **Habicht A**, Bröker V, Blume C, Lorenzen J, Schiffer M, Richter N, Klempnauer J, Haller H, Lehner F, Schwarz A. Increase of infectious complications in ABO-incompatible kidney transplant recipients--a single centre experience. *Nephrol Dial Transplant* 2011; **26**: 4124-4131 [PMID: 21622990 DOI: 10.1093/ndt/gfr215]

47 **Zschiedrich S**, Jänigen B, Dimova D, Neumann A, Seidl M, Hils S, Geyer M, Emmerich F, Kirste G, Drognitz O, Hopt UT, Walz G, Huber TB, Pisarski P, Kramer-Zucker A. One hundred ABO-incompatible kidney transplantations between 2004 and 2014: a single-centre experience. *Nephrol Dial Transplant* 2016; **31**: 663-671 [PMID: 26610596 DOI: 10.1093/ndt/gfv388]

48 **Lopau K**, Syamken K, Rubenwolf P, Riedmiller H, Wanner C. Impact of mycophenolate mofetil on wound complications and lymphoceles after kidney transplantation. *Kidney Blood Press Res* 2010; **33**: 52-59 [PMID: 20197687 DOI: 10.1159/000289573]

49 **Wilpert J**, Fischer KG, Pisarski P, Wiech T, Daskalakis M, Ziegler A, Neumann-Haefelin E, Drognitz O, Emmerich F, Walz G, Geyer M. Long-term outcome of ABO-incompatible living donor kidney transplantation based on antigen-specific desensitization. An observational comparative analysis. *Nephrol Dial Transplant* 2010; **25**: 3778-3786 [PMID: 20466677 DOI: 10.1093/ndt/gfq229]

50 **Masterson R**, Hughes P, Walker RG, Hogan C, Haeusler M, Robertson AR, Millar R, Suh N, Cohney SJ. ABO incompatible renal transplantation without antibody removal using conventional immunosuppression alone. *Am J Transplant* 2014; **14**: 2807-2813 [PMID: 25389083 DOI: 10.1111/ajt.12920]

51 **Kobayashi T**, Liu D, Ogawa H, Miwa Y, Nagasaka T, Maruyama S, Li YT, Onishi A, Kuzuya T, Kadomatsu K, Uchida K, Nakao A. Alternative strategy for overcoming ABO incompatibility. *Transplantation* 2007; **83**: 1284-1286 [PMID: 17496551 DOI: 10.1097/01.tp.0000260634.85690.c4]

52 **Tanabe K**, Ishida H, Inui M, Okumi M, Shirakawa H, Shimizu T, Omoto K, Kondo T. ABO-incompatible kidney transplantation: long-term outcomes. *Clin Transpl* 2013; 307-312 [PMID: 25095522]

53 **Okumi M**, Toki D, Nozaki T, Shimizu T, Shirakawa H, Omoto K, Inui M, Ishida H, Tanabe K. ABO-Incompatible Living Kidney Transplants: Evolution of Outcomes and Immunosuppressive Management. *Am J Transplant* 2016; **16**: 886-896 [PMID: 26555133 DOI: 10.1111/ajt.13502]

54 **Lee EC**, Kim SH, Shim JR, Park SJ. A comparison of desensitization methods: Rituximab with/without plasmapheresis in ABO-incompatible living donor liver transplantation. *Hepatobiliary Pancreat Dis Int* 2018; **17**: 119-125 [PMID: 29576278 DOI: 10.1016/j.hbpd.2018.02.005]

55 **Lo P**, Sharma A, Craig JC, Wyburn K, Lim W, Chapman JR, Palmer SC, Strippoli GF, Wong G. Preconditioning Therapy in ABO-Incompatible Living Kidney Transplantation: A Systematic Review and Meta-Analysis. *Transplantation* 2016; **100**: 933-942 [PMID: 26425876 DOI: 10.1097/TP.0000000000000933]

56 **Takahashi K**, Saito K, Takahara S, Okuyama A, Tanabe K, Toma H, Uchida K, Hasegawa A, Yoshimura N, Kamiryo Y; Japanese ABO-Incompatible Kidney Transplantation Committee. Excellent long-term outcome of ABO-incompatible living donor kidney transplantation in Japan. *Am J Transplant* 2004; **4**: 1089-1096 [PMID: 15196066 DOI: 10.1111/j.1600-6143.2004.00464.x]

57 **Egawa H**, Oike F, Buhler L, Shapiro AM, Minamiguchi S, Haga H, Uryuhara K, Kiuchi T, Kaihara S, Tanaka K. Impact of recipient age on outcome of ABO-incompatible living-donor liver

transplantation. *Transplantation* 2004; **77**: 403-411 [PMID: 14966415 DOI: 10.1097/01.TP.0000110295.88926.5C]

58 **Kimura F**, Sato K, Kobayashi S, Ikeda T, Sao H, Okamoto S, Miyamura K, Mori S, Akiyama H, Hirokawa M, Ohto H, Ashida H, Motoyoshi K; Japan Marrow Donor Program. Impact of AB0-blood group incompatibility on the outcome of recipients of bone marrow transplants from unrelated donors in the Japan Marrow Donor Program. *Haematologica* 2008; **93**: 1686-1693 [PMID: 18835834 DOI: 10.3324/haematol.12933]

59 **Kim JG**, Sohn SK, Kim DH, Baek JH, Lee KB, Min WS, Kim CC, Lee MH, Lee JJ, Chung IJ, Kim HJ, Lee JW. Impact of ABO incompatibility on outcome after allogeneic peripheral blood stem cell transplantation. *Bone Marrow Transplant* 2005; **35**: 489-495 [PMID: 15654350 DOI: 10.1038/sj.bmt.1704816]

60 **Okada M**, Watarai Y, Iwasaki K, Murotani K, Futamura K, Yamamoto T, Hiramitsu T, Tsujita M, Goto N, Narumi S, Takeda A, Morozumi K, Uchida K, Kobayashi T. Favorable results in ABO-incompatible renal transplantation without B cell-targeted therapy: Advantages and disadvantages of rituximab pretreatment. *Clin Transplant* 2017; **31** [PMID: 28792635 DOI: 10.1111/ctr.13071]

61 **Rowley SD**, Liang PS, Ulz L. Transplantation of ABO-incompatible bone marrow and peripheral blood stem cell components. *Bone Marrow Transplant* 2000; **26**: 749-757 [PMID: 11042656 DOI: 10.1038/sj.bmt.1702572]

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MINIREVIEWS

Management of biliary atresia: To transplant or not to transplant

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Abstract

Kasai procedure (KP) and liver transplantation (LT) represent the only therapeutic options for patients with biliary atresia (BA), the most common indication for LT in the pediatric population. However, KP represents by no means a radical option but rather a bridging one, as nearly all patients will finally require a liver graft. More and more experts in the field of transplant surgery propose that maybe it is time for a paradigm change in BA treatment and abandon KP as transplantation seems inevitable. Inadequacy of organs yet makes this option currently not feasible, so it seems useful to find ways to maximize the efficacy of KP. In previous decades, multiple studies tried to identify these factors which opt for better results, but in general, outcomes of KP have not improved to the level that was anticipated. This review provides the framework of conditions which favor native liver survival after KP and the ones which optimize a positive LT outcome. Strategies of transition of care at the right time are also presented, as transplantation plays a key role in the surgical treatment of BA. Future studies and further organization in the transplant field will allow for greater organ availability and better outcomes to be achieved for BA patients.

Key Words: Biliary atresia; Kasai procedure; Portoenterostomy; Native liver survival; Liver transplantation

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Core Tip: Timely diagnosis of biliary atresia (BA) is critical to optimizing the outcomes of Kasai procedure (KP), which should be performed as early as possible. Children with a delayed diagnosis of BA at high risk of early KP failure or those presenting with clear evidence of decompensated cirrhosis should be considered for primary liver transplantation (LT). Early KP failure requiring salvage LT within the first 2-3 years of life occurs in nearly half of all children with BA but even those with a successful KP need life-long monitoring for progression of liver disease that may require salvage LT.

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INTRODUCTION

Biliary atresia (BA) represents the most common indication for pediatric liver transplantation (LT) worldwide, accounting for half of LTs in children and one-tenth of all LTs[1]. Kasai was the first who performed successful drainage of the bile into the intestine after resecting the obliterated extrahepatic portion of the biliary tree[2].

Although the Kasai procedure (KP) is considered to be the first-line treatment, the progressive liver injury seen in most patients with BA results in a 5-year post-procedural native liver survival (NLS) between 38%-40% even at experienced centers [3-5]. As a result, most patients will need a salvage LT (sLT) at some point during their lifetime. The overall low lifetime NLS creates an important dilemma for pediatric LT experts: Should LT be considered primary therapy in infants with BA and a high likelihood of KP failure, or should it be utilized as a salvage therapy? This review aims to highlight the key concepts around this question and to provide an update regarding the management and outcomes of KP and LT for BA.

PATHOPHYSIOLOGY

The pathogenesis of BA is not fully understood but appears to be multifactorial. Approximately 15% of patients with BA have associated congenital malformations, such as abdominal and thoracic heterotaxia, polysplenia, asplenia, and intestinal malrotation[6]. Viruses, such as cytomegalovirus, herpes virus, Epstein-Barr virus, and reovirus, may also contribute to a certain extent in the pathogenesis of BA. Additional factors which may contribute are neonatal immune dysregulation and environmental toxins[7,8]. While radiologic studies, such as hepatobiliary iminodiacetic acid scan, may suggest the diagnosis, failure to visualize the biliary tree during intra-operative cholangiography remains the gold standard for diagnosing BA. Characteristic findings on liver biopsy include edematous fibroplasia with bile ductular proliferation and bile plugs[9].

FACTORS ASSOCIATED WITH NATIVE LIVER SURVIVAL AFTER KASAI

Before the Kasai's report[2], BA was a fatal disease. Unfortunately, KP does not prevent progressive hepatic injury, which gradually leads to cirrhosis and end-stage liver disease (ESLD) in most patients. Numerous studies have attempted to identify the factors predictive of NLS, however, the majority are from single centers and retrospective in nature[1,3,10-15]. Additionally, many of them are limited to univariate analysis, and thus careful interpretation of these results is warranted (Table 1).

The main histologic characteristics of BA are increased cholestasis, marked fibrosis, and ductular proliferation, while the mechanisms behind fibrinogenesis are still under investigation. There seemed to be a clear association between the degree of preoperative fibrosis in the liver biopsy and poor NLS[10,16-18]. Another important histologic finding is intrahepatic duct size, as ducts less than 200 μm represent a risk factor for NLS[19]. However, a large prospective study from 16 centers in North

Table 1 Factors reported to be associated with native liver survival

Before the Kasai procedure	After the Kasai procedure	Other
Liver fibrosis	Jaundice clearance	Specialized institution
Ductal size	Cholangitis	
Biliary atresia type according to Ohi classification	Total bilirubin	
Portal hypertension	Serum creatinine	
Biliary atresia splenic malformation syndrome	Portal hypertension	
Age at the time of Kasai procedure	Serum albumin	
	Corticosteroids	
	Antibiotics	

America found no association between liver fibrosis severity, measured histologically by the 6 grade Ishak score, and NLS. Instead, gross appearance of the liver at the time of surgery was predictive of poor NLS[20]. Regarding BA types based on the Ohi classification, patients with Ohi type 2 and 3 BA appear to have worse outcomes than Ohi type 1[20].

Duché *et al*[21] showed that elevated portal pressure, polysplenia syndrome, and complete atresia of the extrahepatic biliary remnant were independently associated with worse NLS , as there were lower chances of successful postoperative jaundice clearance. The latter is considered extremely important for a proper KP[22,23]. Superina *et al*[20] have also shown the effect of early jaundice clearance on improved NLS. Similar to Duché *et al*[21], Superina *et al*[20] reported the hazardous effect of BA splenic malformation syndrome (BASM) on NLS, which surprisingly was not associated with jaundice clearance after KP. The presence of splenic anomalies as an indicator of poor prognosis has also been documented in other studies[3,24]. The embryological aspects of this malformation have been studied by Davenport *et al*[25] and Karrer *et al*[26], yet the pathogenesis is still unclear. Notably, a study from Sendai, Japan reported similar survival between patients with isolated BA *vs* BA plus BASM and no associated cardiac defects[27]. Sasaki *et al*[28] demonstrated that presence of symptomatic portal hypertension (gastro-esophageal varices requiring treatment), but not hypersplenism nor cholangitis, was found to be a significant risk factor in multivariate logistic regression analysis for NLS.

Age at the time of KP plays a vital role in NLS[5]. There is a general consensus among pediatric surgeons that the sooner the diagnosis and KP is performed, the better the outcome. Several cutoffs between 7-10 wk after birth have been proposed in the literature[3,10,20,29]. It is noteworthy that the age at KP in the United States has not decreased significantly over time[30].

Expertise in KP offered in high-volume centers and centralization of care for patients with BA has been thought of playing a key role in improving outcomes. Although excellent results can be obtained even in centers with relatively little experience[31], this theory seems to have a strong basis[3]. The so-called "center effect" reflects the experience of the teams at individual centers, and in certain countries in Europe (*e.g.*, United Kingdom, Finland) centralization of care to suprare-gional centers has been effective in optimizing outcomes nationwide[32,33].

Regarding postoperative factors, recurrent cholangitis episodes have been associated with KP failure in multiple studies[18,34-36]. More specifically, Wildhaber *et al*[18] demonstrated an approximately double risk for patients with bridging fibrosis and postoperative cholangitis compared to those with cholangitis only, showing the impact of this underlying condition. Moreover, Wu *et al*[35] noted that patients with BA and inadequate bile drainage had more cholangitis episodes than those with adequate bile drainage, while the occurrence of cholangitis was associated with decreased NLS in both groups of patients. In contrast, a single-center study from California showed no association between cholangitis episodes and the need for LT [19], and the same was reported in a more recent study from Japan[28]. It is well-established that BA is an obstructive intra- and extrahepatic cholangiopathy, while KP can only solve the extrahepatic part of the problem. Therefore, for optimal outcomes, KP can be combined with regimes dealing with intrahepatic obstruction, inflam-mation, and bile infection[37]. Specifically, ursodeoxycholic acid has been utilized often for this purpose due to its immunomodulatory and cytoprotective effects[38].

Jain *et al*[39] described several parameters associated with an increased risk for requiring LT after 16 years of age. They reported that among BA patients achieving NLS until the age of 16 years, only serum total bilirubin and creatinine were associated with higher risk of requiring LT. A retrospective study from Australia and Canada showed that a serum albumin level below 35 g/L was a poor prognostic indicator in infants with BA who were no longer jaundiced at 3 mo after KP[40].

Corticosteroids are well-known modulators of BA inflammation as they reduce the production of inflammatory cytokines (tumor necrosis factor-α, interleukin-1, interleukin-8), prostaglandins, and nitric oxide[41]. They also seem to have other choleretic effects, which have not been studied as extensively. Results from early studies on the use of corticosteroids showed a benefit in survival in BA patients[42-45]. A randomized controlled trial from 2007 showed that corticosteroids had a benefit on the rate of reduction of bilirubin early postoperatively, yet they did not reduce the need for LT[46]. The more recent START randomized clinical trial compared 70 children receiving intravenous methylprednisolone (4 mg/kg/d for 2 wk) and oral prednisolone (2 mg/kg/d for 2 wk) followed by a tapering protocol for 9 wk with 70 children receiving placebo initiated within 3 d of KP[47]. The study showed that high-dose steroids after KP did not significantly improve bile drainage at 6 mo, although a small clinical benefit could not be excluded[47]. However, treatment with steroids was associated with earlier onset of serious adverse events[47]. A meta-analysis published in 2015 showed no significant difference in jaundice clearance for patients who received steroids overall; nonetheless, sensitivity analysis excluding studies on the use of high- or low-dose steroids and including only studies on the use of moderate-high dose steroids (prednisolone 4-5 mg/kg/d) showed a higher jaundice clearance rate at 6 mo post-KP[48]. Prednisolone is the most frequently prescribed steroid in most studies, but dexamethasone and hydrocortisone have also been described in the literature[49]. The possible side effects of long-term steroid use should not be neglected.

There is limited knowledge about potential benefit of post-KP use of antibiotics. The commonest intravenous regimen in a survey of European practice is a combination of piperacillin-tazobactam and gentamicin[50]. A randomized clinical trial by Bu *et al*[51] demonstrated a positive impact of post-KP use of trimethoprim–sulfamethoxazole or oral neomycin, while a recent systematic review of four articles by Dechaurun *et al*[52] presented ambiguous results with three studies suggesting the presence of a potential benefit in using antibiotics. The need for high-quality evidence in the form of prospective studies in this field is evident.

LT OUTCOMES

The majority of patients with BA will progress to ESLD requiring evaluation for LT at some point in their life. Since Kasai's first description[2], there have not been significant changes to the technique of KP, and long-term NLS has not significantly improved. Unfortunately, even patients who manage to survive more than 20 years after KP have histological, clinical, or ultrasonographic evidence of significant chronic liver disease[53,54]. Portal hypertension is also commonly observed in BA patients at some point after KP[53,54].

sLT is considered when patients who had undergone KP develop ESLD. A retrospective study from the United States reported a higher incidence of cholangitis, sepsis, and bacteremia in the baseline characteristics of patients who underwent sLT, compared with those who underwent only KP[55]. The authors also compared the outcomes between primary liver transplantation (pLT) and KP, regardless of whether patients eventually required sLT. Early survival was higher in the KP group, but long-term survival was significantly better in pLT group (5-year survival 88% for KP *vs* 94% for pLT)[55]. sLT was also associated with an increased risk of death compared to pLT, which may be attributed to the technical difficulties of sLT in the setting of previous KP and hilar dissection. Recipients of sLT for BA have been reported to have a higher incidence of infectious and vascular complications and intestinal perforation compared to pLT recipients, likely due to previous surgical interventions[56-58]. The incidence of pLT for BA varies from 10%-11% in Canada, Switzerland, and Germany to 3%-4% in the Netherlands, United Kingdom, and France and to 0.1% in Japan[59], so the decision regarding the management of BA may vary among different healthcare systems.

Nevertheless, there are studies reporting equivalent LT outcomes between patients with and without a previous KP. The findings of equivalent post-LT survival

regardless of prior KP support the recommendation for a staged approach for the treatment of BA, starting with KP and progressing to LT only when necessary[60-63]. It is argued that in this way, KP delays the need for LT and allows not only for the improvement of the child's nutritional status but also for their size to increase and to increase the potential size-matched organ donor pool. A multicenter study from 39 centers in the USA and Canada failed to demonstrate an effect of prior KP on LT outcome[64]. Cowles *et al*[65] reported on 71 children who underwent LT for BA, 61 of whom had previously undergone KP, and they observed no clear difference in the outcomes between the two groups. A 2016 meta-analysis reported no difference in 1- and 5-year patient and graft survival between patients who underwent KP and those who did not, yet patients who had undergone KP prior to LT had an increased risk of postoperative infection[66].

Another interesting aspect is the comparison of post-transplant after KP outcomes between children and adults. Kyoden *et al*[67] found no significant differences in survival with a 5-year patient survival of 90% in both age groups, yet a large retrospective study from Japan demonstrated a clear survival benefit in the pediatric population (5-year patient survival 86.7% in children *vs* 69.7% in adults)[68]. In both studies the patients received a living donor graft[67,68]. A more recent single-center study from King's College Hospital also showed superior patient survival after deceased donor LT for BA patients listed as children (n = 22) compared to those listed as adults (n = 14), yet the results did not reach statistical significance because of the limited study sample[69].

The type of liver graft may also be a major prognostic factor. Living donation has expanded the donor pool and also provided recipients with organs which appear to be of better quality than the deceased ones[70]. Multiple studies agree that living donor grafts have superior outcomes in patients with BA[60], but there are also reports challenging this theory[61,63,64]. A study from 1996 had suggested that LT using reduced-size grafts (only part of the donor liver is used for the graft, and the remaining resected liver is discarded) may not be the best option for BA due to inferior outcomes[62]. However, since reduced-size grafts were mostly utilized in emergency situations, the authors stated that after censoring these, they found no significant difference in patient survival between elective reduced-size and whole liver grafts[62]. A more recent study using national registry data showed that the effect of donor allograft is related to recipient weight for children with BA[71]. Specifically, for children ≤ 7 kg, reduced size grafts and living donor grafts had decreased risk of graft failure compared to whole grafts, for children 7-14 kg living donor grafts had decreased risk of graft failure compared to both reduced size and whole grafts, while for children > 14 kg there was no difference in graft failure by allograft type[71].

There are several studies that tried to identify predictors of a successful LT in children with BA (Table 2). Fouquet *et al*[61] demonstrated that BASM, intraoperative complications (hemorrhage, intestinal injury, vascular thrombosis), and hospitalization in the intensive care unit were associated with an increased risk of death. Utterson *et al*[64] reported that infant recipient (≤ 11 mo), use of cyclosporine *vs* tacrolimus, growth deficit, and re-transplantation were associated with post-LT mortality. Living donation, technological refinements, increased surgical experience, and advances in anesthesia and in immunosuppression will play a key role in improving post-LT outcomes.

TRANSITION OF CARE

So, the main question remains: To transplant or not to transplant? For many decades it was considered that KP must be the first choice for patients with BA, serving as a bridging therapy to delay or even avoid the need for LT. Today it is well-established that most BA patients will eventually require LT at some point in their lifetime, yet the demand for donor livers continuously exceeds the supply. LT has matured to the stage where in most centers excellent long-term survival can be achieved despite the technical challenges of sLT following KP. However, the excellent long-term outcomes of pLT suggest this is also a reasonable alternative treatment option for certain patients [59]. pLT is now being more frequently considered for children with BA at a very high likelihood of early failure of KP, challenging the traditional treatment paradigm.

For children who have undergone KP, the best next step is to ensure adequate follow-up and appropriate transition of care from childhood to adulthood so as to continuously monitor for manifestations of ESLD and refer for LT when needed. Progressive jaundice, recurrent bacterial cholangitis, portopulmonary hypertension,

Table 2 Factors associated with liver transplant outcomes

Patient characteristics	Surgical characteristics
Age at the time of liver transplant	Previous Kasai procedure
Biliary atresia splenic malformation	Intraoperative complications (hemorrhage, intestinal injury, vascular thrombosis)
Growth deficit	Allograft type
Hospitalization in the intensive care unit	Re-transplantation
Type of immunosuppression	

and hepatopulmonary syndrome warrant evaluation for LT. Implementation of objective scoring systems, including Model for End-stage Liver Disease and Pediatric End-stage Liver Disease score systems, have decreased the pediatric waitlist mortality and increased the number of patients receiving a deceased donor liver graft[55]. However, several manifestations of ESLD are not adequately reflected in these scoring systems, and thus many children with BA eventually require exception points to undergo LT[72]. Mortality risk has been shifted gradually to the pre-transplant period, and peri-transplant risks are mainly related to patient's condition[73]. Receiving an LT at a young age allows for greater use of left lateral segment graft from a living donor without affecting the deceased donor pool. From another point of view, KP is far more cost-effective compared to pLT[74].

Timely diagnosis of BA is critical to optimizing the outcomes of KP, which should be performed as early as possible. Children with a delayed diagnosis of BA at high risk of early KP failure or those presenting with clear evidence of decompensated cirrhosis should be considered for pLT. Early KP failure requiring sLT within the first 2-3 years of life occurs in nearly half of all children with BA, but even those with a successful KP need life-long monitoring for progression of liver disease that may require sLT.

CONCLUSION

In conclusion, cooperation between pediatric and adult hepatologists, pediatric surgeons, and transplant surgeons is necessary for the management of BA patients. Close and long-term follow-up is required to monitor for manifestations of ESLD that may warrant evaluation for LT, as well as to improve quality of life along with survival outcomes. More prospective multicenter studies are needed to demonstrate a clear conclusion about the proper management of BA.

REFERENCES

1 **Sokol RJ**, Shepherd RW, Superina R, Bezerra JA, Robuck P, Hoofnagle JH. Screening and outcomes in biliary atresia: summary of a National Institutes of Health workshop. *Hepatology* 2007; **46**: 566-581 [PMID: 17661405 DOI: 10.1002/hep.21790]

2 **Kasai M**. A new operation for" non-correctable" biliary atresia: hepatic portoenterostomy. *Shujutsu* 1959; **13**: 733-739

3 **Chardot C**, Buet C, Serinet MO, Golmard JL, Lachaux A, Roquelaure B, Gottrand F, Broué P, Dabadie A, Gauthier F, Jacquemin E. Improving outcomes of biliary atresia: French national series 1986-2009. *J Hepatol* 2013; **58**: 1209-1217 [PMID: 23402746 DOI: 10.1016/j.jhep.2013.01.040]

4 **Bondoc AJ**, Taylor JA, Alonso MH, Nathan JD, Wang Y, Balistreri WF, Bezerra JA, Ryckman FC, Tiao GM. The beneficial impact of revision of Kasai portoenterostomy for biliary atresia: an institutional study. *Ann Surg* 2012; **255**: 570-576 [PMID: 22258066 DOI: 10.1097/SLA.0b013e318243a46e]

5 **Serinet MO**, Wildhaber BE, Broué P, Lachaux A, Sarles J, Jacquemin E, Gauthier F, Chardot C. Impact of age at Kasai operation on its results in late childhood and adolescence: a rational basis for biliary atresia screening. *Pediatrics* 2009; **123**: 1280-1286 [PMID: 19403492 DOI: 10.1542/peds.2008-1949]

6 **Khalil BA**, Perera MT, Mirza DF. Clinical practice: management of biliary atresia. *Eur J Pediatr* 2010; **169**: 395-402 [PMID: 20020156 DOI: 10.1007/s00431-009-1125-7]

7 **Harper P**, Plant JW, Unger DB. Congenital biliary atresia and jaundice in lambs and calves. *Aust Vet J* 1990; **67**: 18-22 [PMID: 2334368 DOI: 10.1111/j.1751-0813.1990.tb07385.x]

8 **Mack CL**, Sokol RJ. Unraveling the pathogenesis and etiology of biliary atresia. *Pediatr Res* 2005; **57**: 87R-94R [PMID: 15817506 DOI: 10.1203/01.PDR.0000159569.57354.47]

9 **Vij M**, Rela M. Biliary atresia: pathology, etiology and pathogenesis. *Future Sci OA* 2020; **6**: FSO466 [PMID: 32518681 DOI: 10.2144/fsoa-2019-0153]

10 **Altman RP**, Lilly JR, Greenfeld J, Weinberg A, van Leeuwen K, Flanigan L. A multivariable risk factor analysis of the portoenterostomy (Kasai) procedure for biliary atresia: twenty-five years of experience from two centers. *Ann Surg* 1997; **226**: 348-353; discussion 353-355 [PMID: 9339941 DOI: 10.1097/00000658-199709000-00014]

11 **Davenport M**, Kerkar N, Mieli-Vergani G, Mowat AP, Howard ER. Biliary atresia: the King's College Hospital experience (1974-1995). *J Pediatr Surg* 1997; 479-485 [PMID: 9094023 DOI: 10.1016/s0022-3468(97)90611-4]

12 **Pietrobattista A**, Mosca A, Liccardo D, Alterio T, Grimaldi C, Basso M, Saffioti MC, Corte CD, Spada M, Candusso M. Does the Treatment After Kasai Procedure Influence Biliary Atresia Outcome and Native Liver Survival? *J Pediatr Gastroenterol Nutr* 2020; **71**: 446-451 [PMID: 32960536 DOI: 10.1097/MPG.0000000000002837]

13 **Wang Z**, Chen Y, Peng C, Pang W, Zhang T, Wu D, Shen Q, Li M. Five-year native liver survival analysis in biliary atresia from a single large Chinese center: The death/liver transplantation hazard change and the importance of rapid early clearance of jaundice. *J Pediatr Surg* 2019; **54**: 1680-1685 [PMID: 30518490 DOI: 10.1016/j.jpedsurg.2018.09.025]

14 **Huang CY**, Chang MH, Chen HL, Ni YH, Hsu HY, Wu JF. Bilirubin level 1 week after hepatoportoenterostomy predicts native liver survival in biliary atresia. *Pediatr Res* 2020; **87**: 730-734 [PMID: 31618755 DOI: 10.1038/s41390-019-0610-6]

15 **Ramos-Gonzalez G**, Elisofon S, Dee EC, Staffa SJ, Medford S, Lillehei C, Kim HB. Predictors of Need for Liver Transplantation in Children Undergoing Hepatoportoenterostomy for Biliary Atresia. *J Pediatr Surg* 2019; **54**: 1127-1131 [PMID: 30879751 DOI: 10.1016/j.jpedsurg.2019.02.051]

16 **Schweizer P**, Schweizer M, Schellinger K, Kirschner HJ, Schittenhelm C. Prognosis of extrahepatic bile-duct atresia after hepatoportoenterostomy. *Pediatr Surg Int* 2000; **16**: 351-355 [PMID: 10955561 DOI: 10.1007/s003830000385]

17 **Weerasooriya VS**, White FV, Shepherd RW. Hepatic fibrosis and survival in biliary atresia. *J Pediatr* 2004; **144**: 123-125 [PMID: 14722530 DOI: 10.1016/j.jpeds.2003.09.042]

18 **Wildhaber BE**, Coran AG, Drongowski RA, Hirschl RB, Geiger JD, Lelli JL, Teitelbaum DH. The Kasai portoenterostomy for biliary atresia: A review of a 27-year experience with 81 patients. *J Pediatr Surg* 2003; **38**: 1480-1485 [PMID: 14577071 DOI: 10.1016/s0022-3468(03)00499-8]

19 **Baerg J**, Zuppan C, Klooster M. Biliary atresia--a fifteen-year review of clinical and pathologic factors associated with liver transplantation. *J Pediatr Surg* 2004; **39**: 800-803 [PMID: 15185199 DOI: 10.1016/j.jpedsurg.2004.02.020]

20 **Superina R**, Magee JC, Brandt ML, Healey PJ, Tiao G, Ryckman F, Karrer FM, Iyer K, Fecteau A, West K, Burns RC, Flake A, Lee H, Lowell JA, Dillon P, Colombani P, Ricketts R, Li Y, Moore J, Wang KS; Childhood Liver Disease Research and Education Network. The anatomic pattern of biliary atresia identified at time of Kasai hepatoportoenterostomy and early postoperative clearance of jaundice are significant predictors of transplant-free survival. *Ann Surg* 2011; **254**: 577-585 [PMID: 21869674 DOI: 10.1097/SLA.0b013e3182300950]

21 **Duché M**, Fabre M, Kretzschmar B, Serinet MO, Gauthier F, Chardot C. Prognostic value of portal pressure at the time of Kasai operation in patients with biliary atresia. *J Pediatr Gastroenterol Nutr* 2006; **43**: 640-645 [PMID: 17130742 DOI: 10.1097/01.mpg.0000235754.14488.f9]

22 **Karrer FM**, Price MR, Bensard DD, Sokol RJ, Narkewicz MR, Smith DJ, Lilly JR. Long-term results with the Kasai operation for biliary atresia. *Arch Surg* 1996; **131**: 493-496 [PMID: 8624194 DOI: 10.1001/archsurg.1996.01430170039006]

23 **McKiernan PJ**, Baker AJ, Lloyd C, Mieli-Vergani G, Kelly DA. British paediatric surveillance unit study of biliary atresia: outcome at 13 years. *J Pediatr Gastroenterol Nutr* 2009; **48**: 78-81 [PMID: 19172128 DOI: 10.1097/MPG.0b013e31817d80de]

24 **Vazquez J**, López Gutierrez JC, Gámez M, López-Santamaría M, Murcia J, Larrauri J, Diaz MC, Jara P, Tovar JA. Biliary atresia and the polysplenia syndrome: its impact on final outcome. *J Pediatr Surg* 1995; **30**: 485-487 [PMID: 7760248 DOI: 10.1016/0022-3468(95)90062-4]

25 **Davenport M**, Savage M, Mowat AP, Howard ER. Biliary atresia splenic malformation syndrome: an etiologic and prognostic subgroup. *Surgery* 1993; **113**: 662-668 [PMID: 8506525]

26 **Karrer FM**, Hall RJ, Lilly JR. Biliary atresia and the polysplenia syndrome. *J Pediatr Surg* 1991; **26**: 524-527 [PMID: 2061801 DOI: 10.1016/0022-3468(91)90697-r]

27 **Nio M**, Wada M, Sasaki H, Tanaka H, Watanabe T. Long-term outcomes of biliary atresia with splenic malformation. *J Pediatr Surg* 2015; **50**: 2124-2127 [PMID: 26613836 DOI: 10.1016/j.jpedsurg.2015.08.040]

28 **Sasaki H**, Tanaka H, Wada M, Kazama T, Nakamura M, Kudo H, Okubo R, Sakurai T, Nio M. Analysis of the prognostic factors of long-term native liver survival in survivors of biliary atresia. *Pediatr Surg Int* 2016; **32**: 839-843 [PMID: 27464487 DOI: 10.1007/s00383-016-3934-x]

29 **Lang T**, Kappler M, Dietz H, Harms HK, Bertele-Harms R. Biliary atresia: which factors predict the success of a Kasai operation? *Eur J Med Res* 2000; **5**: 110-114 [PMID: 10756164]

30 **Raval MV**, Dzakovic A, Bentrem DJ, Reynolds M, Superina R. Trends in age for hepatoportoenterostomy in the United States. *Surgery* 2010; **148**: 785-791; discussion 791-792 [PMID: 20709342 DOI: 10.1016/j.surg.2010.07.028]

31 **Shneider BL**, Brown MB, Haber B, Whitington PF, Schwarz K, Squires R, Bezerra J, Shepherd R, Rosenthal P, Hoofnagle JH, Sokol RJ; Biliary Atresia Research Consortium. A multicenter study of

the outcome of biliary atresia in the United States, 1997 to 2000. *J Pediatr* 2006; **148**: 467-474 [PMID: 16647406 DOI: 10.1016/j.jpeds.2005.12.054]

32 **Davenport M**, Ong E, Sharif K, Alizai N, McClean P, Hadzic N, Kelly DA. Biliary atresia in England and Wales: results of centralization and new benchmark. *J Pediatr Surg* 2011; **46**: 1689-1694 [PMID: 21929975 DOI: 10.1016/j.jpedsurg.2011.04.013]

33 **Lampela H**, Ritvanen A, Kosola S, Koivusalo A, Rintala R, Jalanko H, Pakarinen M. National centralization of biliary atresia care to an assigned multidisciplinary team provides high-quality outcomes. *Scand J Gastroenterol* 2012; **47**: 99-107 [PMID: 22171974 DOI: 10.3109/00365521.2011.627446]

34 **Lünzmann K**, Schweizer P. The influence of cholangitis on the prognosis of extrahepatic biliary atresia. *Eur J Pediatr Surg* 1999; **9**: 19-23 [PMID: 10207698 DOI: 10.1055/s-2008-1072206]

35 **Wu ET**, Chen HL, Ni YH, Lee PI, Hsu HY, Lai HS, Chang MH. Bacterial cholangitis in patients with biliary atresia: impact on short-term outcome. *Pediatr Surg Int* 2001; **17**: 390-395 [PMID: 11527173 DOI: 10.1007/s003830000573]

36 **Koga H**, Wada M, Nakamura H, Miyano G, Okawada M, Lane GJ, Okazaki T, Yamataka A. Factors influencing jaundice-free survival with the native liver in post-portoenterostomy biliary atresia patients: results from a single institution. *J Pediatr Surg* 2013; **48**: 2368-2372 [PMID: 24314172 DOI: 10.1016/j.jpedsurg.2013.08.007]

37 **Sokol RJ**, Mack CL. Optimizing outcomes and bridging biliary atresia into adulthood. *Hepatology* 2005; **41**: 231-233 [PMID: 15657917 DOI: 10.1002/hep.20575]

38 **Balistreri WF**. Bile acid therapy in pediatric hepatobiliary disease: the role of ursodeoxycholic acid. *J Pediatr Gastroenterol Nutr* 1997; **24**: 573-589 [PMID: 9161955 DOI: 10.1097/00005176-199705000-00016]

39 **Jain V**, Burford C, Alexander EC, Sutton H, Dhawan A, Joshi D, Davenport M, Heaton N, Hadzic N, Samyn M. Prognostic markers at adolescence in patients requiring liver transplantation for biliary atresia in adulthood. *J Hepatol* 2019; **71**: 71-77 [PMID: 30876944 DOI: 10.1016/j.jhep.2019.03.005]

40 **Nightingale S**, Stormon MO, O'Loughlin EV, Shun A, Thomas G, Benchimol EI, Day AS, Adams S, Shi E, Ooi CY, Kamath BM, Fecteau A, Langer JC, Roberts EA, Ling SC, Ng VL. Early Posthepatoportoenterostomy Predictors of Native Liver Survival in Biliary Atresia. *J Pediatr Gastroenterol Nutr* 2017; **64**: 203-209 [PMID: 28107282 DOI: 10.1097/MPG.0000000000001289]

41 **Mack CL**, Tucker RM, Sokol RJ, Karrer FM, Kotzin BL, Whitington PF, Miller SD. Biliary atresia is associated with CD4+ Th1 cell-mediated portal tract inflammation. *Pediatr Res* 2004; **56**: 79-87 [PMID: 15128911 DOI: 10.1203/01.PDR.0000130480.51066.FB]

42 **Karrer FM**, Lilly JR. Corticosteroid therapy in biliary atresia. *J Pediatr Surg* 1985; **20**: 693-695 [PMID: 4087100 DOI: 10.1016/s0022-3468(85)80026-9]

43 **Muraji T**, Higashimoto Y. The improved outlook for biliary atresia with corticosteroid therapy. *J Pediatr Surg* 1997; **32**: 1103-1106; discussion 1106-1107 [PMID: 9247243 DOI: 10.1016/s0022-3468(97)90408-5]

44 **Dillon PW**, Owings E, Cilley R, Field D, Curnow A, Georgeson K. Immunosuppression as adjuvant therapy for biliary atresia. *J Pediatr Surg* 2001; **36**: 80-85 [PMID: 11150442 DOI: 10.1053/jpsu.2001.20013]

45 **Meyers RL**, Book LS, O'Gorman MA, Jackson WD, Black RE, Johnson DG, Matlak ME. High-dose steroids, ursodeoxycholic acid, and chronic intravenous antibiotics improve bile flow after Kasai procedure in infants with biliary atresia. *J Pediatr Surg* 2003; **38**: 406-411 [PMID: 12632357 DOI: 10.1053/jpsu.2003.50069]

46 **Davenport M**, Stringer MD, Tizzard SA, McClean P, Mieli-Vergani G, Hadzic N. Randomized, double-blind, placebo-controlled trial of corticosteroids after Kasai portoenterostomy for biliary atresia. *Hepatology* 2007; **46**: 1821-1827 [PMID: 17935230 DOI: 10.1002/hep.21873]

47 **Bezerra JA**, Spino C, Magee JC, Shneider BL, Rosenthal P, Wang KS, Erlichman J, Haber B, Hertel PM, Karpen SJ, Kerkar N, Loomes KM, Molleston JP, Murray KF, Romero R, Schwarz KB, Shepherd R, Suchy FJ, Turmelle YP, Whitington PF, Moore J, Sherker AH, Robuck PR, Sokol RJ; Childhood Liver Disease Research and Education Network (ChiLDREN). Use of corticosteroids after hepatoportoenterostomy for bile drainage in infants with biliary atresia: the START randomized clinical trial. *JAMA* 2014; **311**: 1750-1759 [PMID: 24794368 DOI: 10.1001/jama.2014.2623]

48 **Chen Y**, Nah SA, Chiang L, Krishnaswamy G, Low Y. Postoperative steroid therapy for biliary atresia: Systematic review and meta-analysis. *J Pediatr Surg* 2015; **50**: 1590-1594 [PMID: 26143225 DOI: 10.1016/j.jpedsurg.2015.05.016]

49 **Zhang D**, Yang HY, Jia J, Zhao G, Yue M, Wang JX. Postoperative steroids after Kasai portoenterostomy for biliary atresia: a meta-analysis. *Int J Surg* 2014; **12**: 1203-1209 [PMID: 25224699 DOI: 10.1016/j.ijsu.2014.08.407]

50 **Wong ZH**, Davenport M. What Happens after Kasai for Biliary Atresia? *Eur J Pediatr Surg* 2019; **29**: 1-6 [PMID: 30130826 DOI: 10.1055/s-0038-1668146]

51 **Bu LN**, Chen HL, Chang CJ, Ni YH, Hsu HY, Lai HS, Hsu WM, Chang MH. Prophylactic oral antibiotics in prevention of recurrent cholangitis after the Kasai portoenterostomy. *J Pediatr Surg* 2003; **38**: 590-593 [PMID: 12677572 DOI: 10.1053/jpsu.2003.50128]

52 **Decharun K**, Leys CM, West KW, Finnell SM. Prophylactic Antibiotics for Prevention of Cholangitis in Patients With Biliary Atresia Status Post-Kasai Portoenterostomy: A Systematic Review. *Clin Pediatr (Phila)* 2016; **55**: 66-72 [PMID: 26183324 DOI: 10.1177/0009922815594760]

53 **Lykavieris P**, Chardot C, Sokhn M, Gauthier F, Valayer J, Bernard O. Outcome in adulthood of

biliary atresia: a study of 63 patients who survived for over 20 years with their native liver. *Hepatology* 2005; **41**: 366-371 [PMID: 15660386 DOI: 10.1002/hep.20547]

54 **de Vries W**, Homan-Van der Veen J, Hulscher JB, Hoekstra-Weebers JE, Houwen RH, Verkade HJ; Netherlands Study Group of Biliary Atresia Registry. Twenty-year transplant-free survival rate among patients with biliary atresia. *Clin Gastroenterol Hepatol* 2011; **9**: 1086-1091 [PMID: 21820397 DOI: 10.1016/j.cgh.2011.07.024]

55 **LeeVan E**, Matsuoka L, Cao S, Groshen S, Alexopoulos S. Biliary-Enteric Drainage vs Primary Liver Transplant as Initial Treatment for Children With Biliary Atresia. *JAMA Surg* 2019; **154**: 26-32 [PMID: 30208381 DOI: 10.1001/jamasurg.2018.3180]

56 **Alexopoulos SP**, Merrill M, Kin C, Matsuoka L, Dorey F, Concepcion W, Esquivel C, Bonham A. The impact of hepatic portoenterostomy on liver transplantation for the treatment of biliary atresia: early failure adversely affects outcome. *Pediatr Transplant* 2012; **16**: 373-378 [PMID: 22463739 DOI: 10.1111/j.1399-3046.2012.01677.x]

57 **Neto JS**, Feier FH, Bierrenbach AL, Toscano CM, Fonseca EA, Pugliese R, Candido HL, Benavides MR, Porta G, Chapchap P. Impact of Kasai portoenterostomy on liver transplantation outcomes: A retrospective cohort study of 347 children with biliary atresia. *Liver Transpl* 2015; **21**: 922-927 [PMID: 25832004 DOI: 10.1002/lt.24132]

58 **Sugawara Y**, Makuuchi M, Kaneko J, Ohkubo T, Mizuta K, Kawarasaki H. Impact of previous multiple portoenterostomies on living donor liver transplantation for biliary atresia. *Hepatogastroenterology* 2004; **51**: 192-194 [PMID: 15011862]

59 **Superina R**. Biliary atresia and liver transplantation: results and thoughts for primary liver transplantation in select patients. *Pediatr Surg Int* 2017; **33**: 1297-1304 [PMID: 29030698 DOI: 10.1007/s00383-017-4174-4]

60 **Diem HV**, Evrard V, Vinh HT, Sokal EM, Janssen M, Otte JB, Reding R. Pediatric liver transplantation for biliary atresia: results of primary grafts in 328 recipients. *Transplantation* 2003; **75**: 1692-1697 [PMID: 12777858 DOI: 10.1097/01.TP.0000062570.83203.A3]

61 **Fouquet V**, Alves A, Branchereau S, Grabar S, Debray D, Jacquemin E, Devictor D, Durand P, Baujard C, Fabre M, Pariente D, Chardot C, Dousset B, Massault PP, Bernard D, Houssin D, Bernard O, Gauthier F, Soubrane O. Long-term outcome of pediatric liver transplantation for biliary atresia: a 10-year follow-up in a single center. *Liver Transpl* 2005; **11**: 152-160 [PMID: 15666395 DOI: 10.1002/Lt.20358]

62 **Goss JA**, Shackleton CR, Swenson K, Satou NL, Nuesse BJ, Imagawa DK, Kinkhabwala MM, Seu P, Markowitz JS, Rudich SM, McDiarmid SV, Busuttil RW. Orthotopic liver transplantation for congenital biliary atresia. An 11-year, single-center experience. *Ann Surg* 1996; **224**: 276-284; discussion 284-287 [PMID: 8813256 DOI: 10.1097/00000658-199609000-00004]

63 **Visser BC**, Suh I, Hirose S, Rosenthal P, Lee H, Roberts JP, Hirose R. The influence of portoenterostomy on transplantation for biliary atresia. *Liver Transpl* 2004; **10**: 1279-1286 [PMID: 15376306 DOI: 10.1002/Lt.20234]

64 **Utterson EC**, Shepherd RW, Sokol RJ, Bucuvalas J, Magee JC, McDiarmid SV, Anand R; Split Research Group. Biliary atresia: clinical profiles, risk factors, and outcomes of 755 patients listed for liver transplantation. *J Pediatr* 2005; **147**: 180-185 [PMID: 16126046 DOI: 10.1016/j.jpeds.2005.04.073]

65 **Cowles RA**, Lobritto SJ, Ventura KA, Harren PA, Gelbard R, Emond JC, Altman RP, Jan DM. Timing of liver transplantation in biliary atresia-results in 71 children managed by a multidisciplinary team. *J Pediatr Surg* 2008; **43**: 1605-1609 [PMID: 18778993 DOI: 10.1016/j.jpedsurg.2008.04.012]

66 **Wang P**, Xun P, He K, Cai W. Comparison of liver transplantation outcomes in biliary atresia patients with and without prior portoenterostomy: A meta-analysis. *Dig Liver Dis* 2016; **48**: 347-352 [PMID: 26748427 DOI: 10.1016/j.dld.2015.11.021]

67 **Kyoden Y**, Tamura S, Sugawara Y, Yamashiki N, Matsui Y, Togashi J, Kaneko J, Kokudo N, Makuuchi M. Outcome of living donor liver transplantation for post-Kasai biliary atresia in adults. *Liver Transpl* 2008; **14**: 186-192 [PMID: 18236393 DOI: 10.1002/lt.21344]

68 **Uchida Y**, Kasahara M, Egawa H, Takada Y, Ogawa K, Ogura Y, Uryuhara K, Morioka D, Sakamoto S, Inomata Y, Kamiyama Y, Tanaka K. Long-term outcome of adult-to-adult living donor liver transplantation for post-Kasai biliary atresia. *Am J Transplant* 2006; **6**: 2443-2448 [PMID: 16889600 DOI: 10.1111/j.1600-6143.2006.01487.x]

69 **Samyn M**, Davenport M, Jain V, Hadzic N, Joshi D, Heneghan M, Dhawan A, Heaton N. Young People with Biliary Atresia Requiring Liver Transplantation: A Distinct Population Requiring Specialist Care. *Transplantation* 2019; **103**: e99-e107 [PMID: 30461724 DOI: 10.1097/TP.0000000000002553]

70 **Roberts JP**, Hulbert-Shearon TE, Merion RM, Wolfe RA, Port FK. Influence of graft type on outcomes after pediatric liver transplantation. *Am J Transplant* 2004; **4**: 373-377 [PMID: 14961989 DOI: 10.1111/j.1600-6143.2004.00359.x]

71 **Alexopoulos SP**, Nekrasov V, Cao S, Groshen S, Kaur N, Genyk YS, Matsuoka L. Effects of recipient size and allograft type on pediatric liver transplantation for biliary atresia. *Liver Transpl* 2017; **23**: 221-233 [PMID: 27862929 DOI: 10.1002/lt.24675]

72 **Ziogas IA**, Ye F, Zhao Z, Cao S, Rauf MA, Izzy M, Matsuoka LK, Gillis LA, Alexopoulos SP. Mortality Determinants in Children with Biliary Atresia Awaiting Liver Transplantation. *J Pediatr* 2021; **228**: 177-182 [PMID: 32950533 DOI: 10.1016/j.jpeds.2020.09.005]

73 **de Ville de Goyet Prof J**, Grimaldi C Dr, Tuzzolino F, di Francesco F Dr. A paradigm shift in the

intention-to-transplant children with biliary atresia: Outcomes of 101 cases and a review of the literature. *Pediatr Transplant* 2019; **23**: e13569 [PMID: 31410937 DOI: 10.1111/petr.13569]

74 **Raghu VK**, Squires JE, Mogul DB, Squires RH, McKiernan PJ, Mazariegos GV, Smith KJ. Cost-Effectiveness of Primary Liver Transplantation Versus Hepatoportoenterostomy in the Management of Biliary Atresia in the United States. *Liver Transpl* 2021; **27**: 711-718 [PMID: 33460529 DOI: 10.1002/lt.25984]

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