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Epididymitis, orchitis, and epididymo-orchitis associated with SARS-CoV-2 infection in pediatric patients: A systematic review

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Introduction: Epididymitis, orchitis, and epididymo-orchitis (EO) are common disorders in pediatric patients which may be caused by infection, trauma, or inflammation. SARS-CoV-2 associated EO has been previously described, particularly in adults. However, no systematic reviews of these manifestations in pediatric patients yet exist. We present a systematic literature review of epididymitis, orchitis, and EO associated with SARS-CoV-2 in pediatric patients to shed light on these relatively rare, yet potentially severe, conditions to understand presentation, course of illness, management options, and outcomes.

Materials and Methods: Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, a systematic review was performed using specified key terms to search PubMed, Cumulative Index to Nursing and Allied Health Literature, Web of Science, and Embase. Articles were independently screened by two reviewers. Manuscripts with detailed descriptions of SARS-CoV-2 associated epididymitis, orchitis, or EO in pediatric patients were included. Exclusion criteria included: no clear diagnosis of the target diseases and no detailed clinical course described. Quality and bias were assessed using the Joanna Briggs Institute Critical Appraisal Checklist for Case Reports.

Results: 60 records were initially identified, with 6 case reports included in the systematic review. All 6 patients included presented with fever and genitourinary symptoms. Four patients were also diagnosed with multisystem inflammatory syndrome in children (MIS-C). One patient underwent surgical exploration for presumed testicular torsion, though intraoperatively there was no evidence of torsion. All patients recovered without documented long-term sequelae.

Discussion: While observational studies are prone to bias, this systematic review suggests that epididymitis, orchitis, and EO are significant

manifestations of SARS-CoV-2 that may mimic urologic emergencies (i.e., testicular torsion). Providers should suspect these conditions in pediatric COVID-19 patients with scrotal symptoms, particularly with associated MIS-C. The long-term genitourinary sequelae of SARS-CoV-2 should be investigated, including the effects on pediatric patients undergoing reproductive development.

KEYWORDS

epididymitis, orchitis, epididymo-orchitis, pediatric, SARS-CoV-2, multisystem inflammatory syndrome in children, MIS-C

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for the Coronavirus Disease 2019 (COVID-19) pandemic, is associated with a wide variety of pathologic manifestations across multiple organ systems (1–4). Although it is most known for its pulmonary involvement with potential for severe pneumonia and acute respiratory distress syndrome, SARS-CoV-2 also commonly affects the gastrointestinal and cardiovascular systems and can cause widespread systemic inflammatory conditions (1–4). In pediatric patients, these systemic conditions include a Kawasaki Disease-like syndrome with characteristic cutaneous involvement (5, 6). This condition was eventually termed multisystem inflammatory syndrome in children (MIS-C) (5, 6). Several mechanisms for these inflammatory syndromes have been presented including widespread microvascular damage and thrombosis, increased inflammatory mediators (angiotensin II), and extensive immune cell activation (4, 6).

Urologic manifestations of SARS-CoV-2 in adult and pediatric patients

COVID-19 is associated with a variety of urologic manifestations in adult patients. The most common urologic complication of COVID-19 is acute kidney injury with a prevalence of 7.58%, while other less common genitourinary sequelae in adults include ischemic priapism, lower urinary tract dysfunction, and epididymo-orchitis (EO) (7–9). However, the current literature is lacking with respect to the viruses' urologic effect in pediatric COVID-19 patients. Recently published case reports of ischemic priapism in a 12-year-old boy and torsion of appendix testis in an 8-year-old boy provide some insight into the genitourinary manifestations of SARS-CoV-2 (10, 11). Additionally, there have been some reports of EO associated with SARS-CoV-2 in pediatric patients. However, no systematic reviews of the genitourinary manifestations of SARS-CoV-2 within the pediatric patient, specifically EO, currently exist.

Abbreviations: ACE2, angiotensin converting enzyme 2; EO, Epididymitis-orchitis; MIS-C, multisystem inflammatory syndrome in children; PRISMA, Preferred Reporting Items for Systematic Reviews; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; TMPRSS2, Transmembrane serine protease 2.

Epididymitis, orchitis, and epididymo-orchitis in pediatric patients

Epididymitis is defined as inflammation of the epididymis, orchitis is defined as inflammation of the testis, and EO is defined as the presence of both epididymitis and orchitis (12–14). These conditions most commonly present with scrotal pain, redness, and swelling, and ultrasound findings characteristically include enlargement of the testis and/or epididymis, thickening of the tunica albuginea, and increased flow on Doppler ultrasound (12–15). The incidence of EO has been estimated at 1.2 out of 1,000 annually in boys aged 2-14 years old, while a recent review of retrospective studies on epididymitis and EO indicated a mean incidence of 37.3% in pediatric patients presenting with an acute scrotum (16, 17). EO may be caused by a variety of etiologies, including infection (*Chlamydia trachomatis, Neisseria gonorrhea*, tuberculosis, mumps), medications (amiodarone), and systemic inflammatory conditions such as Kawasaki Disease, Henoch-Schoenlein Purpura, and, most recently, SARS-CoV-2 related MIS-C (12–14, 18, 19). In addition to acute and systemic inflammation, SARS-CoV-2 may also directly infect cells of the testis *via* its functional receptor angiotensin converting enzyme 2 (ACE2) (20). ACE2 is also expressed in testicular tissue, suggesting a potential novel pathophysiologic mechanism of EO (20).

Given that SARS-CoV-2 may directly infect the genitourinary tract and may cause systemic inflammation, particularly within the pediatric population, epididymitis,

orchitis, and EO are uncommon but significant manifestations in pediatric patients. Herein, we present a systematic review of the known pediatric cases of epididymitis, orchitis, and EO associated with COVID-19. Our objective is to investigate the clinical presentations of cases, including initial signs and symptoms, subsequent management, and outcomes in pediatric patients with concurrent COVID-19 infection and epididymitis, orchitis, and EO.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were utilized to systematically query databases from inception through April 2022. Databases searched were PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, and Embase, to access cases of epididymitis, orchitis, and EO associated with COVID-19 (21). Key terms utilized for PubMed, CINAHL, Web of Science, and Embase were "((epididymitis) OR (orchitis) OR (Orchiepididymitis) OR (epididymorchitis) OR (epidiymo*)) AND ((covid*) OR (coronavirus) OR (SARS-CoV-2)) AND ((pediatric*) OR (paediatric*) OR (child*) OR (adolesc*))". No additional filters or restrictions were utilized for any of the databases. Additional references deemed relevant to our systematic review were obtained through cross-references. For a more detailed description of our search strategies, please see Supplementary Table 1 which details our search criteria for each database, as well as our protocol in the supplementary files.

For this systematic review, inclusion criteria consisted of articles that provided a detailed description of epididymitis, orchitis, or EO associated with COVID-19 in pediatric patients aged 18 years and under. The target outcomes and data collected for comparison are detailed in Table 1 and include the presenting symptoms, examination findings, diagnostic results, therapeutic management, and clinical outcomes. Manuscripts were excluded if: a) there was no clear diagnosis epididymitis, orchitis, or EO, b) there was no association with COVID-19, c) the relevant patients were greater than 18 years old, or d) the study in question did not contain a detailed description of the patient's clinical course including initial presentation, management, and clinical outcome.

The included studies were assessed for quality and bias utilizing the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports (22). Missing data was recorded as "not reported" and excluded from the syntheses when appropriate. Two authors independently completed the systematic review to determine article eligibility, collect data, and perform initial qualitative synthesis. Any discrepancies between the two reviewers were discussed among the study team to reach a consensus. While this study was not registered through PROSPERO as data collection began prior to registration, a protocol detailing the methodology of this systematic review was created and is available in the supplementary files.

Results

Study selection

Our initial query using the previously described search criteria produced 60 results (Figure 1). After 21 duplicates were removed, the remaining 39 results were screened based on title and abstract for the inclusion criteria, resulting in 7 manuscripts appropriate for full text review. An additional 4 manuscripts were found based on cross-referencing, resulting in a total of 11 manuscripts for full text review. Of the 11 reviewed, 5 articles were excluded resulting in 6 case reports for subsequent synthesis (Table 1) (23–28). Two manuscripts were excluded due to no clear diagnosis in a case series, and 3 manuscripts were excluded as they described retrospective cohorts without detailed clinical courses (5, 19, 29–31).

Initial presentation and diagnosis

The 6 case reports included in this systematic literature review described a total of 6 male patients with a mean age of 9.5 years (range 5-14). All 6 reports fulfilled all 8 items of the JBI Critical Appraisal Checklist for Case Reports. Table 1 describes the clinical characteristics of the 6 patients included in this systematic review. All 6 patients had fever and genitourinary symptoms on initial presentation, while 5 patients had documented testicular or scrotal swelling subjectively. Onset of any symptom of SARS-CoV-2 to presentation was on average 4 days (range 2-8), while onset of genitourinary symptoms to presentation was on average 3.5 days (range 2-8) (Table 2). One patient experienced possible prodromal symptoms with 2 days of high fever that spontaneously resolved 2 weeks prior to admission. One patient was diagnosed with acute epididymitis and 5 patients were diagnosed with EO. Physical exam findings commonly included scrotal swelling, erythema, and tenderness. All patients were admitted to the hospital for their conditions.

Five patients had confirmed COVID-19 *via* nasopharyngeal reverse transcription polymerase chain reaction (RT-PCR). 1 patient was negative for SARS-CoV-2 on nasopharyngeal RT-PCR though had a positive anti-SARS-CoV-2 IgG with a confirmed positive sick-contact (Table 2). Four of the 6 cases were associated with MIS-C. All 6 patients had documented hematologic derangements, including either leukocytosis, lymphopenia, or lymphopenic leukocytosis. Additionally, all 6 patients had elevated inflammatory markers, most commonly C-reactive protein and erythrocyte sedimentation rate, though procalcitonin, ferritin, and D-dimer were also elevated in some patients. Of the 5 cases with documented urine studies

TABLE 1 Included cases of epididymitis, orchitis, and epididymo-orchitis associated with COVID-19 in pediatric patients.

Authors, Year	Age (years)	Diagnosis	MIS-C	Symptoms	Physical Exam	SARS-CoV-2 Testing	Laboratory Values	Ultrasound Findings	Treatment
Rivera-Figueroa et al., 2020	5	Epididymo-orchitis associated with Incomplete Kawasaki disease	Y	8 days of fever, rash, swelling of the palms and soles, conjunctivitis Dysuria	Hypotension, cracked and erythematous lips, non-exudative conjunctivitis, cervical lymphadenopathy; no genitourinary exam findings were reported	Positive *via* RT-PCR *via* nasopharyngeal swab	Leukocytosis, anemia, thrombocytopenia Elevated inflammatory markers (ESR, CRP, procalcitonin, ferritin) No urine studies reported Positive rapid streptococcal antigen test at PCP 4 days prior	Right scrotal edema and hydrocele	Initially treated with cefdinir for positive rapid streptococcal antigen test IVIG with diphenhydramine and methylprednisolone pre-treatment, aspirin
Gagliardi et al., 2020	14	Epididymo-orchitis associated with SARS-CoV-2	N	2 days of fever 2 weeks before initial presentation that spontaneously resolved 2 days of right testicular pain and swelling and fever, no urinary symptoms	Massive tense right scrotal swelling	Positive *via* RT-PCR *via* nasopharyngeal swab	Leukocytosis with lymphopenia Elevated inflammatory markers (CRP, IL-6) Normal urinalysis and urine culture Negative viral studies (adenovirus, CMV, EBV, mumps, coxsackie virus), negative *Mycoplasma pneumoniae*	Right testis swelling with increased flow signal *via* color Doppler, inflammation of the epididymis with reactive hydrocele No signs of torsion of the testis or appendix	Initially treated with amoxicillin/clavulanic acid by PCP Broad spectrum antibiotics inpatient (specific medications were not reported)
Gümüşer Cinni et al., 2021	8	Epididymitis associated with MIS-C	Y	4 days of fever 2 days of scrotal pain and swelling, no urinary symptoms or urethral discharge	Scrotal swelling and erythema with diffuse scrotal tenderness. Rash, conjunctival injection, abdominal tenderness	Negative *via* RT-PCR *via* nasopharyngeal swab Positive anti-SARS-CoV-2 IgG	Lymphopenia, thrombocytopenia Elevated inflammatory markers (CRP, ESR, procalcitonin, ferritin, fibrinogen, IL-6) Normal urinalysis and urine culture Negative serologic studies for EBV, CMV, *Mycoplasma pneumoniae*, *Brucella*	Right epididymis with enlargement and hypervascularity and minimal reactive hydrocele	Ceftriaxone, IVIG, methylprednisone
Haydar et al., 2021	7	Epididymo-orchitis associated with MIS-C	Y	3 days of fever, abdominal pain, anorexia, fatigue 2 days of bilateral testicular discomfort	Left scrotal redness, warmth and swelling, testicular tenderness and pain relieved with elevation Red congested oral mucosa, dry cracked lips, rash, diffuse abdominal tenderness	Positive *via* RT-PCR *via* nasopharyngeal swab	Lymphopenia Elevated inflammatory markers (CRP, D-dimer, procalcitonin, ferritin) Normal urinalysis ASO negative	Small clear fluid effusion in the scrotum, testis with hypoechogenic spots, and epididymal edema with an enlarged caput	Ceftriaxone, vancomycin, methylprednisolone, prednisolone, omeprazole, IVIG, aspirin, enoxaparin, dopamine, acetaminophen

(Continued)

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TABLE 1 Continued

Authors, Year	Age (years)	Diagnosis	MIS-C	Symptoms	Physical Exam	SARS-CoV-2 Testing	Laboratory Values	Ultrasound Findings	Treatment
Sudeep et al., 2021	9	Epididymo-orchitis associated with MIS-C	Y	5 days of fever 5 days of scrotal pain and swelling	Scrotal tenderness, swelling, and erythema Fever, shock, rash, non-suppurative conjunctivitis	Positive *via* RT-PCR *via* nasopharyngeal swab	Leukocytosis, lymphopenia Elevated inflammatory markers Negative urine cultures Negative blood cultures and anti-mumps antibody	Increased testicular volume with increased flow, inflammation of the epididymis No evidence of testicular or appendix torsion	Antibiotics (specific medications were not reported), IVIG, methylprednisolone, prednisolone, aspirin, vasoactive drugs
Wronowski et al., 2021	14	Epididymo-orchitis associated with SARS-CoV-2	N	2 days of fever, mild cough 2 days of anorectal pain, vesical tenesmus, testicular swelling, dysuria, urinary frequency	Enlarged and painful testicles right greater than left	Positive *via* RT-PCR *via* nasopharyngeal swab	Leukocytosis Elevated inflammatory markers (CRP) Urinalysis with leukocytes and leukocyte aggregates (no urine culture was reported)	Initial: Testicular torsion Repeat: Thickening of the tunica albuginea, vasitis, and epididymitis	Cefuroxime axetil by PCP for cystitis, surgical revision of scrotum, ceftriaxone and oral levofloxacin

ASO, Antistreptolysin O.; CMV, Cytomegalovirus; CRP, C-reactive protein; EBV, Epstein-Barr Virus; ESR, Erythrocyte sedimentation rate; IL-6, Interleukin 6; IVIG, Intravenous immunoglobulin; MIS-C, Multisystem inflammatory syndrome in children; PCP, Primary care provider; PICU, pediatric intensive care unit; RT-PCR, Reverse transcriptase polymerase chain reaction; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.

(urinalysis or urine culture), only 1 urinalysis was positive for leukocytes and leukocyte aggregates in a patient experiencing dysuria and urinary frequency; no urine culture results were reported for this patient and SARS-CoV-2 RT-PCR of his urine was negative. Five out of 6 patients had additional infectious studies documented including viral serologies (Epstein-Barr Virus, Cytomegalovirus, *Mycoplasma pneumoniae*), antistreptolysine O, and blood cultures. Other than one patient with a positive outpatient rapid streptococcal antigen test, all other infectious studies were negative. For all 6 patients, no sexually transmitted infection testing was reported (i.e., *Chlamydia trachomatis, Neisseria gonorrhoeae*), and there were no comments documented on the patients' sexual activity. Scrotal ultrasounds were performed on all 6 patients to support the diagnoses, with common findings including increased testicular volume, hypervascularity, and reactive hydrocele. Interestingly, 1 patient had an initial ultrasound which revealed "testicular torsion" prompting surgical intervention, though during scrotal exploration, no torsion was found (28). The initial ultrasound findings to suggest torsion were not described in the case report, and repeat ultrasound showed findings more consistent with EO with thickening of the tunica albuginea and vasitis.

Management and outcomes

Treatment for all cases of epididymitis, orchitis, and EO included antibiotics most commonly with a third-generation cephalosporin (cefdinir, ceftriaxone), though other antibiotics utilized include cefdinir, vancomycin, and levofloxacin (Table 1). Two patients were treated prior to admission with antibiotics prescribed by their primary care physicians (cefuroxime and amoxicillin/clavulanic acid). All cases associated with MIS-C were treated with intravenous immunoglobulin (IVIG) and methylprednisolone, though other medications included aspirin, proton pump inhibitors (omeprazole), vasoactive medications (dopamine), and anti-coagulants (enoxaparin, heparin). All patients were hospitalized with a mean hospital stay of 7.5 days (range 3-10). 2 patients reportedly required admission to the pediatric intensive care unit (PICU) for hemodynamic instability, and all patients eventually recovered from their illness with no mortalities. Only 2 cases indicated any follow-up after admission, with Gagliardi et al. describing "progression to normality" at 8 days after discharge and Sudeep et al. reporting their patient was asymptomatic at 1 month follow-up.

Discussion

Cases in this systematic review

To our knowledge, this is the first systematic review to critically evaluate the published cases of epididymitis, orchitis, and EO

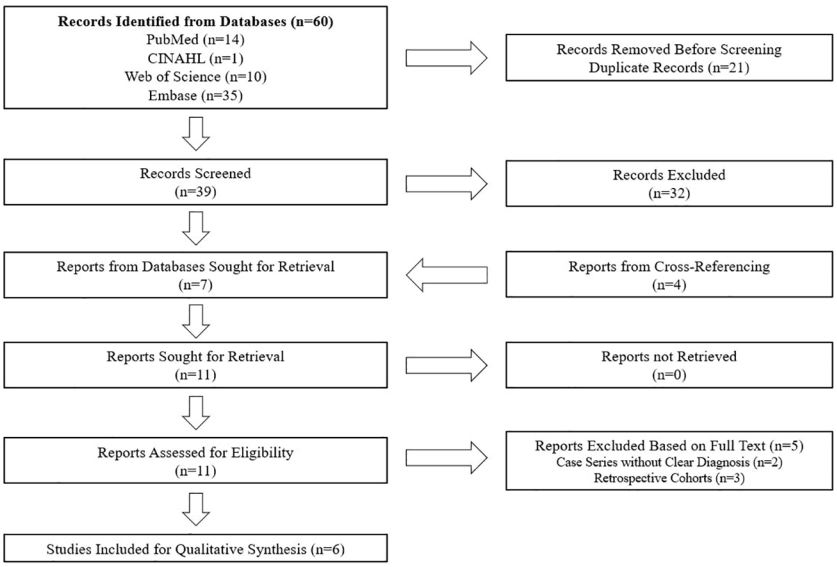

FIGURE 1
PRISMA flowchart for systematic review process. CINAHL, Cumulative Index to Nursing and Allied Health Literature.

associated with COVID-19 in pediatric patients. Along with the 6 cases described in this systematic review, our literature search also resulted in 1 case of epididymitis, 2 cases of orchitis, and 1 case of EO documented across three retrospective cohorts of pediatric patients with COVID-19, though these cases were excluded in the present systematic review due to lack of detailed information regarding symptomatology, management, and outcomes (5, 30, 31). Although relatively few cases have been reported since the beginning of the COVID-19 pandemic, the cases included in this systematic review were severe and associated with complex COVID-19, each requiring at least 6 days of admission. Additionally, given the nature of case reports which typically

TABLE 2 Clinical features of epididymitis, orchitis, and epididymo-orchitis associated with COVID-19 in pediatric patients.

Case Information	Proportion of Patients (Percent) or Mean (Range)
Age (years)	9.5 (5-14)
Diagnosis	
Epididymitis	1
Orchitis	0
Epididymo-orchitis	5
Symptom onset of COVID-19 symptoms to presentation (days)	4 (2-8)
SARS-CoV-2 confirmed:	
via RT-PCR by nasopharyngeal swab	5/6 (83.3%)
via anti-SARS-CoV-2 IgG	1/6 (16.7%)
Association with MIS-C	4/6 (66.7%)
Treated with antibiotics	6/6 (100%)
Treated with surgery	1/6 (16.7%)
Admission to PICU	2/6 (33.3%)
Length of admission (days)	8.5 (6-10)
Recovered at discharge	6/6 (100%)

MIS-C, Multisystem inflammatory syndrome in children; PICU, pediatric intensive care unit; RT-PCR, Reverse transcriptase polymerase chain reaction.

describe the most severe cases, there may be many children who experience relatively mild symptoms at home without contacting their health care providers. All patients survived and were discharged in significantly improved conditions.

SARS-CoV-2 and MIS-C

The majority of the cases included in our systematic review were associated with MIS-C. Additionally, all 4 of the previously mentioned cases excluded (due to insufficient data) were associated with MIS-C (5, 30, 31). Furthermore, we also reviewed 2 pediatric case series in MIS-C patients which described 2 patients with signs and symptoms of epididymitis, orchitis, and EO. This included scrotal pain in one patient and signs of hyperemia of the testes and epididymes in the other patient (19, 29). In consideration of these factors, male patients with MIS-C should be carefully monitored for genitourinary symptoms. Epididymitis, orchitis, and EO should be considered as possible diagnoses in COVID-19 patients with urinary or scrotal symptoms.

SARS-CoV-2 and molecular mechanisms related to EO

Epididymitis, orchitis, and EO in pediatric patients are relatively common conditions potentially caused by infection, reflux or stasis of urine, trauma, or systemic inflammatory conditions. SARS-CoV-2 may be another causative virus due to a combination of cellular susceptibility to infection and systemic inflammation. Similar to its predecessor SARS-CoV-1, SARS-CoV-2 uses ACE2 as its functional receptor and transmembrane serine protease 2 (TMPRSS2) for priming its spike protein (32, 33). In human tissues, ACE2 is highly expressed in the lungs, oral and nasal mucosae, and within the gastrointestinal tract, suggesting potential sites of initial infection and routes of transmission (32, 33). Furthermore, the distribution of ACE2 and TMPRSS2 expression correlates with common sequelae of COVID-19, including within the respiratory system (cough, rhinorrhea, pneumonia) and gastrointestinal system (vomiting, diarrhea) (32). ACE2 and TMPRSS2 have been shown to be expressed within the testis including in Sertoli cells, Leydig cells, and spermatogonia, suggesting potential susceptibility of these cells to direct COVID-19 (20, 34).

SARS-CoV-2 and the male reproductive system

Along with the biomolecular susceptibility of the male reproductive system, several objective laboratory and radiologic findings are associated with COVID-19. In a cohort of adult male patients with confirmed COVID-19 at single center in Wuhan, China, 32/142 (22.5%) met ultrasonographic diagnostic criteria of epididymitis, orchitis, or EO (15). Autopsy studies of patients infected with SARS-CoV-2 showed findings consistent with interstitial orchitis as well evidence of germ cell infection with scarcity of Sertoli and Leydig cells and decreased spermatogenesis (35, 36). Several studies have found hormonal derangements in patients infected with SARS-CoV-2, with increasing severity of infection associated with increasing magnitude of hormonal change (37, 38). Furthermore, certain etiologies of epididymitis, orchitis, and EO are associated with chronic and irreversible sequelae including infertility due to germ cell destruction and damage to the seminiferous tubules including mumps and chronic *C. trachomatis and N. gonorrhoeae* (12, 14, 39). While SARS-CoV-2 is not known to cause irreversible infertility, it has demonstrated an ability to alter sperm analyses with effects on sperm motility and sperm count (40). In light of this, within the pediatric population, the potential for COVID-19 to adversely affect sexual development and puberty should be considered, and future investigations assessing long-term outcomes in this developing population are warranted.

SARS-CoV-2 in Urology and future directions

Along with the previously published cases of ischemic priapism and torsion of the appendix testis, SARS-CoV-2 may present with multiple acute genitourinary symptoms and may even mimic acute urologic emergencies, as exemplified by the case in this systematic review who underwent surgical exploration for suspected testicular torsion. Providers should be cognizant of the urologic manifestations of SARS-CoV-2 in pediatric patients and have a high suspicion for epididymitis, orchitis, or EO in pediatric SARS-CoV-2 patients with genitourinary symptoms, particularly in the setting of MIS-C. Future investigations should be directed towards exploring the long-term sequelae of COVID-19 within the genitourinary tract, including the potential effects on male fertility. Furthermore, consideration of these factors may be taken when counseling pediatric patients and their families regarding immunization against SARS-CoV-2.

Limitations

Limitations of this study include the descriptive observational nature of case reports and case series which are, by nature, prone to biases. Furthermore, as previously described, case reports and case series often display the most severe clinical courses seen at academic centers, and it is possible that more benign cases of epididymitis, orchitis, and EO are occurring in the general population without medical evaluation. This

systematic review also includes a relatively small number of included articles which may limit the generalizability. However, the complications investigated in this study are relatively rare and the long-term effects of COVID-19 on sexual development in pediatric patients still need to be elucidated; therefore, this systematic review of the published cases is warranted to assemble and synthesize the limited data regarding this clinically significant manifestation. Our systematic review was also not registered through PROSPERO as data collection had begun prior to registration, though we followed the guidelines to the best of our ability and have uploaded our PRISMA checklist and protocol in the supplementary files.

Conclusion

SARS-CoV-2 may increase the risk of epididymitis, orchitis, and EO due to its capacity to cause systemic inflammation as well as the biomolecular mechanisms involving ACE2 and TMPRSS2. In pediatric patients with COVID-19 who are experiencing genitourinary symptoms, clinicians should have a high suspicion for epididymitis, orchitis, and EO, especially in those with concurrent MIS-C. Further research regarding the urologic sequelae of SARS-CoV-2 is warranted, particularly with respect to the long-term reproductive health of infected pediatric patients who are undergoing reproductive development.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

All authors conceptualized the study design. DI and ZB conducted the review with oversight from EV and AP. DI was primarily responsible for writing the manuscript, with additional input from ZB and AP and revisions from EV. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fruro.2022.1092192/full#supplementary-material

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