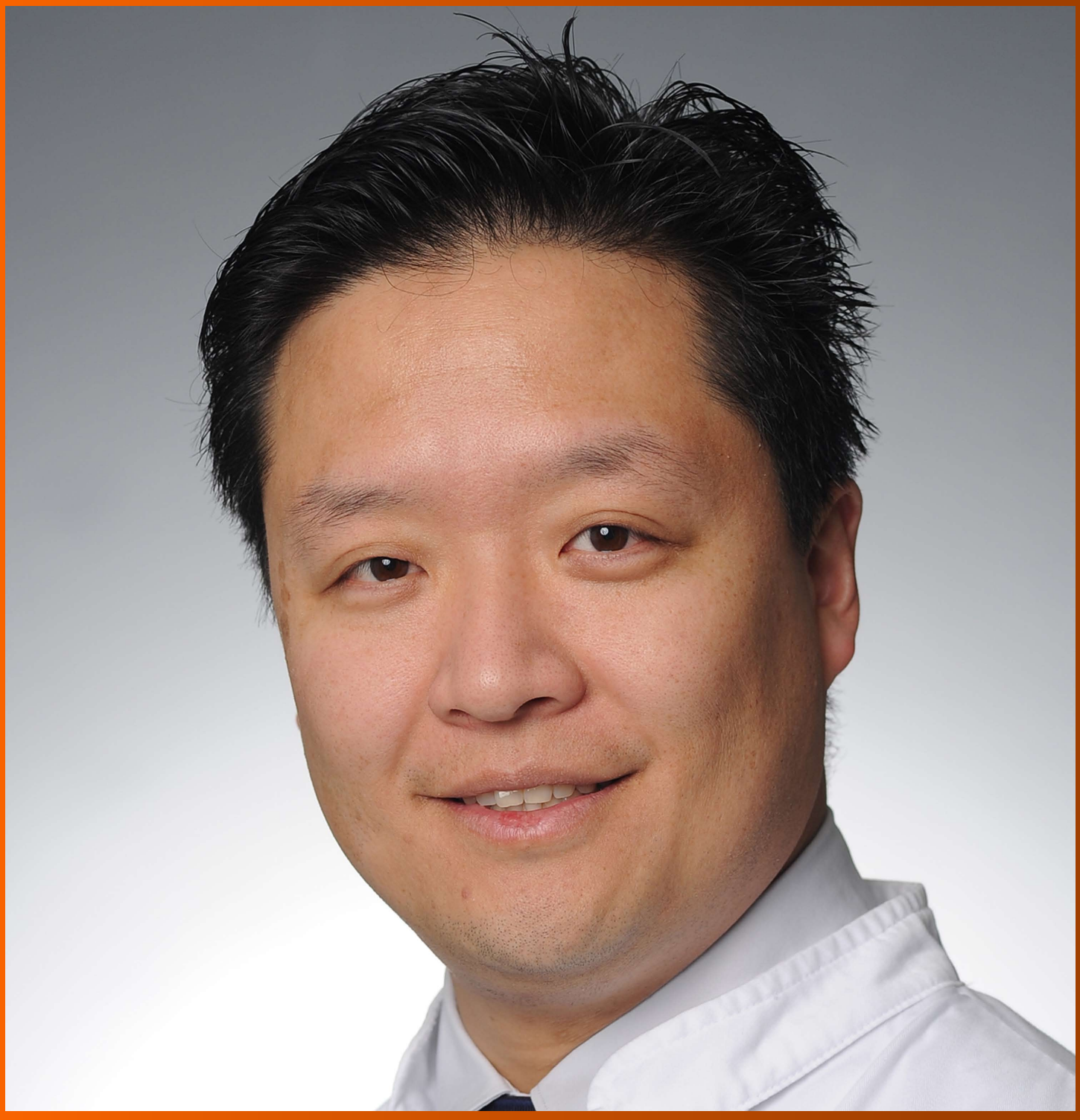
ISSN 2219-2808 (online)

World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2017 May 8; 6(2): 110-131



Published by Baishideng Publishing Group Inc

WJCP World Journal of Clinical Pediatrics

A peer-reviewed, online, open-access journal of clinical pediatrics

Editorial Board

2017-2020

The *World Journal of Clinical Pediatrics* Editorial Board consists of 262 members, representing a team of worldwide experts in pediatrics. They are from 44 countries, including Argentina (1), Australia (7), Austria (4), Belgium (3), Brazil (4), Canada (8), Chile (2), China (25), Denmark (2), Egypt (9), Finland (1), France (6), Germany (5), Greece (6), India (19), Indonesia (1), Iran (6), Israel (7), Italy (24), Japan (7), Mexico (2), Netherlands (2), New Zealand (1), Nigeria (3), Norway (1), Pakistan (2), Poland (2), Portugal (1), Romania (1), Russia (2), Saudi Arabia (2), Serbia (2), Singapore (3), Slovenia (1), South Africa (2), South Korea (3), Spain (3), Sri Lanka (2), Sweden (4), Switzerland (1), Thailand (3), Tunisia (1), Turkey (20), United Arab Emirates (2), United Kingdom (9), United States (39), and Viet Nam (1).

South Korea

Byung-Ho Choe, *Daegu*
Dong-Hee Lee, *Seoul*
Eell Ryoo, *Incheon*

Spain

Juan F Martinez-Lage Sanchez, *Murcia*
Pablo Menendez, *Andalucía*
Juan A Tovar, *Madrid*

Sri Lanka

Niranga Manjuri Devanarayana, *Ragama*
Shaman Rajindrajith, *Ragama*

Sweden

Moustapha Hassan, *Stockholm*
Maria C Jenmalm, *Linkoping*
Sandra Kleinau, *Uppsala*
Birgitta Lindberg, *Lulea*

Switzerland

Ulf Kessler, *Bern*

Thailand

Surasak Sangkhathat, *Songkhla*
Duangrurdee Wattanasirichaigoon, *Bangkok*
Viroj Wiwanitkit, *Bangkok*

Tunisia

John C Anyanwu, *Tunis*

Turkey

Sinem Akgul, *Ankara*
Berna Aksoy, *Kocaeli*
Ayse T Altug, *Ankara*
Nur Arslan, *Izmir*
Suna Asilsoy, *Adana*
Ozgu Aydogdu, *Nigde*
Kadir Babaoglu, *Kocaeli*
Murat Biteker, *Mugla*
Merih Cetinkaya, *Bursa*
Aynur E Cicekcibasi, *Konya*
Elvan C Citak, *Mersin*
Cem Dane, *Istanbul*
Mintaze K Gunel, *Ankara*
Ahmet Guzel, *Samsun*
Sabri Herguner, *Konya*
Salih Kavukcu, *Balcova Izmir*
Fethullah Kenar, *Denizli*
Selim Kurtoglu, *Kayseri*
Turker M Ozyigit, *Istanbul*
Yalcin Tüzün, *Istanbul*

United Arab Emirates

Iradj Amirlak, *Al Ain*
Dimitrios Papandreou, *AbuDhabi*

United Kingdom

Keith Collard, *Plymouth*
A Sahib M El-Radhi, *London*
Edzard Ernst, *Exeter*
Mohammad K Hajihosseini, *Norwich*
Tain-Yen Hsia, *London*
Cordula M Stover, *Leicester*
Alastair G Sutcliffe, *London*
Richard Trompeter, *London*
Petros V Vlastarakos, *Stevenage*

United States

Stephen C Aronoff, *Philadelphia*
Hossam M Ashour, *Detroit*
Paul Ashwood, *Sacramento*
David C Bellinger, *Boston*
Vineet Bhandari, *New Haven*
Francisco R Breijo-Marquez, *Boston*
Patrick D Brophy, *Hawkins Drive Iowa*
Dorothy I Bulas, *Washington*
Lavjay Butani, *Sacramento*
Archana Chatterjee, *Omaha*
Lisa M Cleveland, *San Antonio*
Christopher L Coe, *Madison*
Shri R Deshpande, *Atlanta*
Michael M Dowling, *Dallas*
Abdulrahman M El-Sayed, *Detroit*
Donald N Forthal, *Atlanta*
Gregory K Friedman, *Birmingham*
Kenneth W Gow, *Seattle*
Elias Jabbour, *Houston*
Michael VD Johnston, *Baltimore*
Ram V Kalpatthi, *Kansas City*
Stephen S Kim, *Annandale*
Edward Y Lee, *Boston*
Jing Lin, *New York*
Jorge Lopez, *Ann Arbor*
Murielle Mimeault, *Omaha*
Natan Noviski, *Boston*
Michael D Seckeler, *Charlottesville*
Chetan C Shah, *Little Rock*
Anurag Singh, *Buffalo*
Mohamed Tarek M Shata, *Cincinnati*
Tsz-Yin So, *Greensboro*
Ru-Jeng Teng, *Wauwatosa*
Rajan Wadhawan, *St.Petersburg*
Hongjun Wang, *Charleston*
Richard Wang, *Atlanta*
Wladimir Wertelecki, *Mobile*
Shu Wu, *Miami*
Fadi Xu, *Albuquerque*

Viet Nam

Nguyen V Bang, *Hanoi*

WJCP

World Journal of Clinical Pediatrics

Contents

Quarterly Volume 6 Number 2 May 8, 2017

ORIGINAL ARTICLE

Retrospective Study

Observational Study

World Journal of Clinical Pediatrics
Volume 6 Number 2 May 8, 2017

Contents

NAME OF JOURNAL
World Journal of Clinical Pediatrics

ISSN
ISSN 2219-2808 (online)

LAUNCH DATE
June 8, 2012

FREQUENCY
Quarterly

EDITORIAL OFFICE
Xiu-Xia Song, Director
World Journal of Clinical Pediatrics
Baishideng Publishing Group Inc
7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
May 8, 2017

INSTRUCTIONS TO AUTHORS
http://www.wjgnet.com/bpg/gerinfo/204

ONLINE SUBMISSION
http://www.f6publishing.com

World Journal of Clinical Pediatrics

Submit a Manuscript: http://www.f6publishing.com

World J Clin Pediatr 2017 May 8; 6(2): 110-117

DOI: 10.5409/wjcp.v6.i2.110

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Retrospective Study

Conversion from prolonged intravenous fentanyl infusion to enteral methadone in critically ill children

Vijay Srinivasan, Daniel Pung, Sean P O'Neill

Vijay Srinivasan, Department of Anesthesiology and Critical Care Medicine, the Children's Hospital of Philadelphia, Philadelphia, PA 19104, United States

Vijay Srinivasan, Department of Anesthesiology, Critical Care and Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, United States

Daniel Pung, Department of Pharmacy Services, Children's Hospital of New Jersey at Newark Beth Israel Medical Center, Newark, NJ 07112, United States

Sean P O'Neill, Office of Patient Safety and Quality, the Children's Hospital of Philadelphia, Philadelphia, PA 19104, United States

Author contributions: Srinivasan V, Pung D and O'Neill SP contributed equally to this work and approve the final version of this submitted manuscript; Srinivasan V is the guarantor and designed the study; Srinivasan V, Pung D and O'Neill SP participated in the acquisition, analysis and interpretation of data; Srinivasan V drafted the initial manuscript; Srinivasan V, Pung D and O'Neill SP revised the manuscript critically for important intellectual content.

Supported by Russell Raphaely Endowed Chair Funds in Critical Care Medicine, the Children's Hospital of Philadelphia, Philadelphia, PA, No. 08-005894.

Institutional review board statement: The study was reviewed and approved by the Institutional Review Board at the Children's Hospital of Philadelphia (CHOP IRB Research Protocol 08-3-5894).

Informed consent statement: Informed consent and assent was waived by the Institutional Review Board at the Children's Hospital of Philadelphia due to the retrospective nature of the observational study and analysis of only de-identified subject data.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

Correspondence to: Vijay Srinivasan, MD, FCCM, Department of Anesthesiology and Critical Care Medicine, the Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104, United States. srinivasan@email.chop.edu
Telephone: +1-215-5905505
Fax: +1-215-5904327

Received: January 7, 2017
Peer-review started: January 10, 2017
First decision: February 17, 2017
Revised: March 4, 2017
Accepted: March 23, 2017
Article in press: March 24, 2017
Published online: May 8, 2017

Abstract

AIM

To describe our institutional experience with conversion from intravenous (IV) fentanyl infusion directly to enteral methadone and occurrence of withdrawal in critically ill mechanically ventilated children exposed to prolonged sedation and analgesia.

METHODS

With Institutional Review Board approval, we retrospectively studied consecutively admitted invasively mechanically ventilated children (0-18 years) sedated with IV fentanyl infusion > 5 d and subsequently converted directly to enteral methadone. Data were obtained on

subject demographics, illness severity, daily IV fentanyl and enteral methadone dosing, time to complete conversion, withdrawal scores (WAT-1), pain scores, and need for rescue opioids. Patients were classified as rapid conversion group (RCG) if completely converted ⩽ 48 h and slow conversion group (SCG) if completely converted in > 48 h. Primary outcome was difference in WAT-1 scores at 7 d. Secondary outcomes included differences in overall pain scores, and differences in daily rescue opioids.

RESULTS

Compared to SCG (n = 21), RCG (n = 21) had lower median WAT-1 scores at 7 d (2.5 *vs* 5, P = 0.027). Additionally, RCG had lower overall median pain scores (3 *vs* 6, P = 0.007), and required less median daily rescue opioids (3 *vs* 12, P = 0.003) than SCG. The starting daily median methadone dose was 2.3 times the daily median fentanyl dose in the RCG, compared to 1.1 times in the SCG (P = 0.049).

CONCLUSION

We observed wide variation in conversion from IV fentanyl infusion directly to enteral methadone and variability in withdrawal in critically ill mechanically ventilated children exposed to prolonged sedation. In those children who converted successfully from IV fentanyl infusion to enteral methadone within a period of 48 h, a methadone:fentanyl dose conversion ratio of approximately 2.5:1 was associated with less withdrawal and reduced need for rescue opioids.

Key words: Methadone; Withdrawal; Children; Intensive care; Prolonged opioid infusion

Core tip: Critically ill children exposed to prolonged opioid infusions for sedation and analgesia frequently experience withdrawal symptoms when these infusions are discontinued. Conversion to intermittent opioids such as methadone may reduce such withdrawal symptoms, but published studies and guidelines vary widely in terms of dosing and timeframes for such conversions. In this pragmatic analysis of current practice in our institution, we observed wide variation in dosing conversion and timeframes. We observed that it is feasible to convert from intravenous fentanyl infusion directly to enteral methadone within a timeframe of 48 h using a methadone:fentanyl dose conversion ratio of approximately 2.5:1 to minimize withdrawal and reduce need for rescue opioids.

Srinivasan V, Pung D, O'Neill SP. Conversion from prolonged intravenous fentanyl infusion to enteral methadone in critically ill children. *World J Clin Pediatr* 2017; 6(2): 110-117 Available from: URL: http://www.wjgnet.com/2219-2808/full/v6/i2/110.htm DOI: http://dx.doi.org/10.5409/wjcp.v6.i2.110

INTRODUCTION

Children admitted to the pediatric intensive care unit (PICU) are often administered opioids in the form of intravenous (IV) infusions to provide consistent sedation and analgesia titrated to effect[1,2]. Tolerance and physical dependence frequently develop with prolonged opioid use resulting in an increased likelihood of developing a withdrawal syndrome when the IV opioid infusion is abruptly discontinued[3]. Withdrawal is frequently associated with neurologic, autonomic and gastrointestinal abnormalities, which can result in considerable morbidity with prolongation of PICU and hospital length of stay[4]. The risk of withdrawal increases depending on the cumulative dose exposure as well as the duration of infusion[3,4]. For example, a cumulative IV fentanyl dose of at least 1.5 milligrams per kilogram (mg/kg) or 5 d of IV infusion has been associated with a 50% risk of developing withdrawal symptoms when the IV fentanyl infusion was rapidly weaned over 2 d[4]. This risk increases to 100% when the patient has received a cumulative dose of at least 2.5 mg/kg or 9 d of continuous IV fentanyl infusion[4]. Withdrawal may be avoided or attenuated during recovery either by slowly tapering the IV infusion, or by conveniently substituting the IV opioid infusion with IV or enteral opioids that are then tapered slowly over a period of time.

Methadone is a commonly used synthetic opioid for weaning critically ill children off IV opioid infusions due to its long half-life, good oral bioavailability and low cost[5-9]. Methadone is available for administration in both IV and enteral forms. However, concerns with use of methadone include lack of pharmacokinetic data in children, significant interactions with other drugs, and increased risk of electrocardiographic abnormalities such as QT_c prolongation[10-12]. Importantly, there is a lack of consensus on an optimal dosing guideline for conversion from IV fentanyl infusions directly to enteral methadone (or *via* IV methadone as an intermediate step). A variety of studies have documented varying methadone:fentanyl conversion ratios (ranging from 1:1 to 4:1) and time frames (ranging from 24-48 h or longer) during conversion from IV fentanyl infusion to enteral methadone[6-9,13-16]. We undertook this study to describe our institutional experience with conversion from IV fentanyl infusion directly to enteral methadone and occurrence of withdrawal in critically ill children exposed to prolonged IV fentanyl infusion for sedation and analgesia. A secondary objective of our study was to derive an optimal dose conversion ratio of methadone: fentanyl associated with minimal withdrawal when converting from IV fentanyl infusion completely and directly to enteral methadone within a 48-h timeframe.

MATERIALS AND METHODS

Study design

With Institutional Review Board approval and waiver

of informed consent, we retrospectively reviewed the medical records of consecutive children admitted to our PICU between November 2004 and February 2008. Patients were included if they were between 0-18 years of age, invasively mechanically ventilated *via* endotracheal tube or tracheostomy, on IV fentanyl infusion for more than 5 d and started on scheduled enteral methadone with the intention to wean off the IV fentanyl infusion completely. Patients with "Do not attempt resuscitation" status, burns, malignancy, chronic pain syndromes, or prior opioid use for more than 7 d in the 3 mo preceding admission to the PICU were excluded. Children undergoing cardiac surgery and neonates are cared for in other intensive care units separate from the PICU at our institution and were not eligible for this study. The pharmacy computer system database and the hospital electronic health record systems were screened for eligible subjects. Data collected included demographic information on age, weight, gender and diagnoses, severity of illness expressed as pediatric risk of mortality (PRISM Ⅲ) scores[17], daily IV fentanyl and enteral methadone dosing, duration and adjustments of IV fentanyl infusion, time to conversion from IV fentanyl infusion to enteral methadone, administration of opioid rescues, and use of concomitant sedative and analgesic medications (benzodiazepines, barbiturates, clonidine, acetaminophen, non-steroidal anti-inflammatory drugs, and neuromuscular blockers).

All patients were monitored for opioid withdrawal symptoms using the Withdrawal Assessment Tool-Version 1 (WAT-1)[18]. The WAT-1 scale ranges from 0 to 12, with higher scores indicating more withdrawal symptoms. All patients were also monitored for pain during this period using pain scales depending on patient age and verbal/cognitive capacity: We used the Face, Legs, Activity, Cry, and Consolability scale in nonverbal children 0 to 6 years of age; the Individualized Numeric Rating Scale in nonverbal cognitively impaired children aged 6 years or older; and the Wong-Baker Faces Pain Scale in verbal children aged 3 years or older[19-21]. All pain scales range from 0 to 10, with higher scores indicating more pain. Data on WAT-1 scores were abstracted at 12, 24, 48, 72, 96 h and 7 d from the time of enteral methadone initiation. Data on overall pain scores were abstracted during the 7 d from initial enteral methadone initiation.

Institutional practice during study period

During the study period, critically ill children requiring invasive mechanical ventilation in our PICU were typically provided sedation and analgesia with IV fentanyl infusions in combination with other agents. Patients who were administered IV fentanyl infusions for prolonged periods (typically greater than 5 d) were usually switched to enteral methadone administered every 12 h during recovery to manage dependence and prevent symptoms of withdrawal. The initial dose conversion from IV fentanyl infusion to enteral methadone was determined by the clinical team based on clinical judgment and in discussion with the Clinical Pharmacist. The suggested time frame for conversion from IV fentanyl infusion to enteral methadone was usually 48 h, but was not standardized and left to attending physician discretion. After the second dose of enteral methadone, the IV fentanyl infusion was decreased by 50%. After the third dose of enteral methadone, the IV fentanyl infusion was decreased by a further 50%. After the fourth dose of enteral methadone, the IV fentanyl infusion was typically discontinued. Thereafter, the dosing of enteral methadone was adjusted by the attending physician to prevent both withdrawal symptoms as well as over-sedation.

Definitions and outcomes

Patients were classified into the rapid conversion group (RCG) if they were completely converted from IV fentanyl infusion to enteral methadone in 48 h or less, or the slow conversion group (SCG) if they were completely converted from IV fentanyl infusion to enteral methadone in more than 48 h. The primary outcome measure was difference in WAT-1 scores between the RCG and the SCG at 7 d from the time of enteral methadone initiation. Secondary outcome measures were differences in WAT-1 scores at 12, 24, 48, 72 and 96 h from the time of enteral methadone initiation, as well as overall WAT-1 and overall pain scores during the 7 d from enteral methadone initiation. Additional secondary outcomes included differences in ventilator free days at 28 d (VFD), PICU length of stay (LOS), and use of daily rescue opioids and concomitant medications.

Statistical analysis

Statistical analysis was performed using Stata 12.0 software (StataCorp, College Station, TX). Standard descriptive summaries were reported for baseline demographic data. The data were presented as mean ± SD if normally distributed, or median with inter-quartile range (IQR) if not normally distributed. Differences between the RCG and the SCG were compared using the *t*-test (in the case of continuous variables that were normally distributed) or the Mann-Whitney *U* test (in the case of continuous variables that were not normally distributed). Differences in categorical variables were compared using the χ^2 test or Fisher's exact test. Differences at respective paired time points for WAT-1 and pain scores between the RCG and the SCG were compared using the Mann-Whitney *U* test (as these were rank ordered). A *P*-value of less than 0.05 was considered statistically significant. Statistical methods and analysis were completed by Srinivasan V (first author of the study and trained in analytical methods *via* University of Pennsylvania biostatistics certificate courses).

RESULTS

A total of forty-two children were included in the study: 21 (50%) in the RCG and 21 (50%) in the SCG. The

Table 1 Baseline characteristics of rapid and slow conversion groups

	Rapid conversion group[a] (n = 21)	Slow conversion group[b] (n = 21)	P value
Age, yr (median, IQR)	1 (0.3-3.5)	2 (0.8-4)	0.95
Gender, male (%)	14 (67%)	9 (43%)	0.21
Weight, kg (median, IQR)	10 (5.5-14.3)	9.6 (6.8-15.9)	0.88
PRISM Ⅲ (mean ± SD)	11.4 ± 9	16.1 ± 9.9	0.13
Admitting diagnosis, n (%)			1
ARDS/acute lung injury	14 (67)	14 (67)	
Other (sepsis, seizures)	7 (33)	7 (33)	
Pre-existing tracheostomy, n (%)	6 (29)	6 (29)	1
Duration of IV fentanyl infusion prior to initiation of enteral methadone, d (median, IQR)	9 (8-14)	10 (8-21)	0.48
Maximum dose of IV fentanyl infusion, μg/kg per hour (median, IQR)	6 (4-7)	6.75 (4-9.25)	0.41
Cumulative dose of IV fentanyl infusion at time of initiation of enteral methadone, mg/kg (median, IQR)	1.48 (1.11-1.92)	1.64 (1.03-1.98)	0.49
Concomitant sedative and analgesic infusions			0.61
Benzodiazepine, n (%)	18 (86)	20 (95)	
Ketamine, n (%)	0 (0)	0 (0)	
Dexmedetomidine, n (%)	0 (0)	0 (0)	

[a]Rapid conversion group: Patients who were completely converted from IV fentanyl infusion directly to enteral methadone in 48 h or less; [b]Slow conversion group: Patients who were completely converted from IV fentanyl infusion directly to enteral methadone in more than 48 h. IQR: Inter-quartile range; SD: Standard deviation; PRISM Ⅲ: Pediatric risk of mortality; ARDS: Acute respiratory distress syndrome; IV: Intravenous.

median time to complete conversion from IV fentanyl infusion to enteral methadone in the RCG was 25 h (IQR 19-34 h), while the median time to complete conversion in the SCG was 109 h (IQR 77-240 h, P < 0.05). Both groups were comparable with regard to baseline characteristics, including severity of illness and admitting diagnosis (Table 1). There were no significant differences in initial fentanyl infusion dose, duration of fentanyl infusion, maximum dose of fentanyl infusion or cumulative dose of fentanyl prior to conversion between the two groups. Table 2 compares the two groups during conversion from IV fentanyl infusion to enteral methadone. Compared with the SCG, the RCG required fewer rescue opioids in the first 96 h of transition per patient and fewer increases in the scheduled dose of enteral methadone. There were no significant differences between the use of concomitant sedative and analgesic medications across the groups.

The initial daily median enteral methadone dose was 2.3 times the daily median IV fentanyl dose in the RCG, compared to 1.1 times in the SCG (P < 0.05). Both groups had similar daily doses of enteral methadone at initiation (0.064 mg/kg in the RCG *vs* 0.06 mg/kg in the SCG, P = 0.62) and at 48 h (0.064 mg/kg in the RCG *vs* 0.076 mg/kg in the SCG, P = 0.9). However, at 7 d, the RCG had a significantly lower daily dose of enteral methadone compared to the SCG (0.03 mg/kg *vs* 0.189 mg/kg, P = 0.02) (Figure 1A). While the RCG experienced a consistent reduction in the IV fentanyl infusion dropping to zero by 48 h, the SCG experienced an increase in the IV fentanyl infusion over the first 48 h followed by a consistent reduction thereafter (Figure 1B).

For the primary outcome measure of withdrawal at 7 d, the RCG had lower median WAT-1 scores at 7 d (2.5 *vs* 5, P = 0.03) (Figure 2). Secondary outcome measures differed between RCG and SCG for: Lower median WAT-1 scores at 48 h (5.5 *vs* 9, P = 0.04), lower overall median WAT-1 scores (5 *vs* 6, P = 0.03) and lower overall median pain scores (3 *vs* 6, P < 0.05). There were no significant differences between RCG and SCG for median WAT-1 scores at 12, 24, 72 and 96 h. Additionally, the RCG had significantly more VFD and shorter PICU LOS than the SCG (Table 3).

DISCUSSION

Critically ill children are at high risk of dependence and withdrawal after prolonged IV opioid infusion use for sedation and analgesia[3]. A significant withdrawal syndrome may occur if IV opioid infusions are abruptly discontinued resulting in considerable morbidity with prolongation of intensive care dependency. Such withdrawal may be minimized, or prevented by a variety of methods including gradually reducing the IV opioid infusion, conversion of the IV opioid infusion to intermittent IV dosing, and conversion of IV opioid infusions to enteral opioids followed by a gradual taper. In this paper, we report the results of our institutional experience with the conversion of IV fentanyl infusion directly to enteral methadone and occurrence of subsequent withdrawal in critically ill mechanically ventilated children receiving prolonged sedation. We observed wide variability in conversion from IV fentanyl infusion directly to enteral methadone and variability in withdrawal in critically ill mechanically ventilated children exposed to prolonged sedation. We also observed that in the subset of children who converted completely from IV fentanyl infusion directly to enteral methadone within a period of 48 h, a methadone:fentanyl dose conversion ratio of approximately 2.5:1 was associated with less withdrawal

Table 2 Conversion from intravenous fentanyl infusion to enteral methadone in rapid and slow conversion groups

	Rapid conversion group[a] (n = 21)	Slow conversion group[b] (n = 21)	P value
Dose of IV fentanyl infusion at initiation of enteral methadone, μg/kg per hour (median, IQR)	4 (3-4)	4.5 (3.6-7)	0.23
Adjustments in scheduled enteral methadone dose			< 0.05
Increase in dose	15	33	
Decrease in dose	17	3	
Opioid rescues in first 96 h of transition per patient (median, IQR)	3 (1-7)	12 (4-17)	< 0.05
0-24 h	0 (0-2)	3 (0-4)	< 0.05
24-48 h	1 (0-2)	2 (1-6)	0.02
48-72 h	0 (0-1)	1 (1-6)	0.01
72-96 h	0 (0-2)	2 (0-4)	0.12
Opioid rescues in first 96 h of transition by agent			< 0.05
Morphine	44	51	
Fentanyl	51	210	
Concomitant medications administered in first 96 h of transition (number of administrations)			0.6
Benzodiazepines	32	40	
Clonidine	5	3	
Barbiturates	2	8	
NSAIDS	2	2	
Neuromuscular blockers	4	6	
Acetaminophen	9	10	

[a]Rapid conversion group: Patients who were completely converted from IV fentanyl infusion directly to enteral methadone in 48 h or less; [b]Slow conversion group: Patients who were completely converted from IV fentanyl infusion directly to enteral methadone in more than 48 h. IV: Intravenous; IQR: Inter-quartile range; NSAIDS: Non-steroidal anti-inflammatory drugs.

Table 3 Clinical outcomes in rapid and slow conversion groups

	Rapid conversion group[a] (n = 21)	Slow conversion group[b] (n = 21)	P value
Ventilator free days at 28 d, d (median, IQR)	18 (13.3-18.8)	8 (1.5-10.8)	< 0.05
Total PICU length of stay, d (median, IQR)	17 (12-24)	38.5 (24.8-68.5)	0.05

[a]Rapid conversion group: Patients who were completely converted from IV fentanyl infusion directly to enteral methadone in 48 h or less; [b]Slow conversion group: Patients who were completely converted from IV fentanyl infusion directly to enteral methadone in more than 48 h. IQR: Inter-quartile range; PICU: Pediatric intensive care unit.

and reduced need for rescue opioids.

Guidelines and studies describing the conversion of IV opioid infusions such as fentanyl to enteral opioids such as methadone often differ with respect to optimal conversion dose, frequency and duration of therapy[6-9,13-16]. One such published guideline recommends a 1:1 dose conversion of IV fentanyl directly to enteral methadone over a period of 48 h to prevent withdrawal from dependence[13]. Another institutional policy recommends a 2.5:1 conversion ratio from IV fentanyl to IV methadone initially and subsequently to enteral methadone once patients tolerate oral intake[14]. These differences in formulation and dosing of methadone at the time of conversion in these studies and guidelines serve to highlight the paucity of knowledge and likely reflect differences in patient profiles, individual pharmacokinetic variation, and prescriber characteristics.

Previous studies have largely focused on transitioning from IV opioid infusions to IV methadone as an intermediate step before transitioning over to enteral methadone[6,7,9]. In contrast, the findings from our study establish that it is feasible to convert from IV fentanyl infusion directly to enteral methadone within a 48 h time period. Table 4 provides an example using data from our study to illustrate dose conversion using a methadone: fentanyl ratio of 2.5:1. Lugo *et al*[8] also studied such a direct conversion to enteral methadone, but employed a fixed methadone dose of 0.1 mg/kg administered enterally every 6 h for conversion regardless of IV fentanyl infusion dose at the time of conversion. A direct conversion has the advantage of reducing the need for continued IV access with the potential to decrease IV catheter infiltrates (in the case of peripheral IV catheters) and catheter-associated complications such as infections and thrombosis (in the case of central IV catheters). Additionally, such a strategy can favorably influence hospital admission costs by reducing the overall duration of PICU and hospital LOS as further weaning of enteral medications can take place either on the general floor or even at home[22].

In the present study, we included critically ill children with a high likelihood of opioid dependence from exposure to IV fentanyl infusion for greater than 5 d who were converted directly to enteral methadone. Methadone is

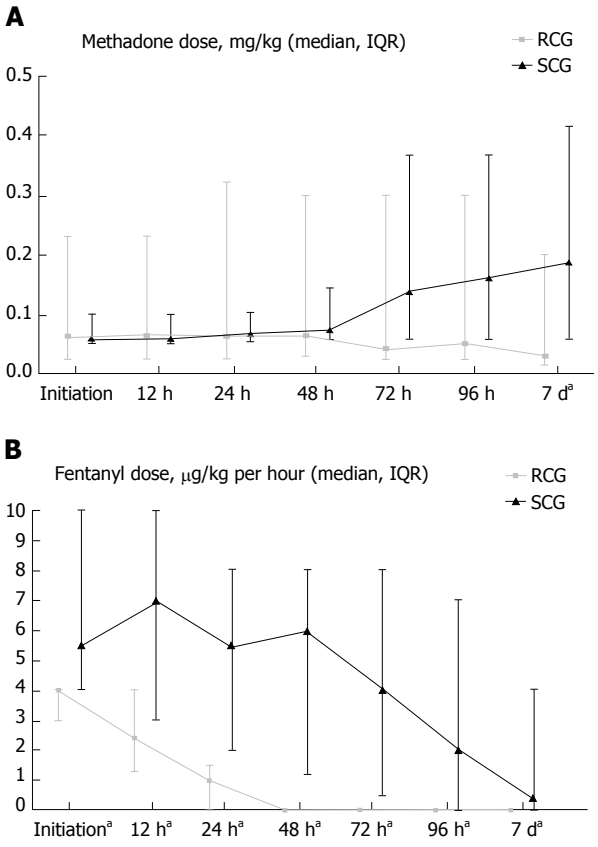


Figure 1 Comparison of enteral methadone and intravenous fentanyl titration across groups in the study. A: Paired comparison of median enteral methadone doses (mg/kg) between rapid conversion group and slow conversion group at serial time points following initiation of enteral methadone ([a]*P* < 0.05); B: Paired comparison of median intravenous fentanyl infusion doses (μg/kg per hour) between rapid conversion group and slow conversion group at serial time points following initiation of enteral methadone ([a]*P* < 0.05). RCG: Rapid conversion group consisted of patients who were completely converted from fentanyl infusion directly to enteral methadone in 48 h or less; SCG: Slow conversion group consisted of patients who were completely converted from fentanyl infusion directly to enteral methadone in more than 48 h.

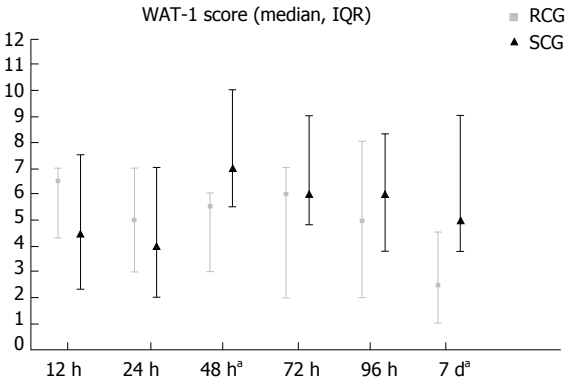


Figure 2 Paired comparison of median withdrawal (Withdrawal Assessment Tool-Version 1) scores between rapid conversion group and slow conversion group at serial time points following initiation of enteral methadone ([a]*P* < 0.05). RCG: Rapid conversion group consisted of patients who were completely converted from fentanyl infusion directly to enteral methadone in 48 h or less; SCG: Slow conversion group consisted of patients who were completely converted from fentanyl infusion directly to enteral methadone in more than 48 h. WAT-1: Withdrawal Assessment Tool-Version 1.

a commonly used synthetic enteral opioid to prevent opioid withdrawal in our unit due to its long mean elimination half-life in children (19 ± 14 h, range 4-62 h), good oral bioavailability (70% to 100%), low cost and ease of tapering[5-9]. Even though the suggested time frame for conversion was 48 h, we observed that only half the patients (RCG) were converted within this time period (in the absence of a unit specific protocol). This variation may have been due to patient factors such as intercurrent illness or perception of pain that may have influenced the conversion. Additionally, prescribing providers might have been anxious about possible withdrawal symptoms due to the perceived rapid time frame for conversion. Consequently, it is possible that in the RCG patients, providers preferentially used a higher dose of enteral methadone during conversion from IV fentanyl infusions to alleviate such concerns. In the other half of patients (SCG), the approximately 1:1 dose conversion required a longer time frame for conversion (median time of 109 h) raising the possibility that the dose of methadone was inadequate to prevent withdrawal. However, several confounding factors could have delayed the conversion in this group, including co-morbidities and intercurrent procedures that we were unable to adjust for in our analyses due to the small sample size. The SCG group was also observed to have an increase in the IV fentanyl infusion within the first 48 h of conversion, and ultimately ended up with a higher daily median methadone dose compared with the RCG (0.189 mg/kg *vs* 0.03 mg/kg, *P* = 0.02) which could possibly reflect an attempt to "catch-up" with withdrawal and pain symptoms.

Importantly, when compared to the SCG patients, the RCG patients were observed to have more ventilator free days and shorter PICU length of stay. While association does not imply causation, it is possible that the "higher" initial dose conversion in the RCG minimized withdrawal during conversion and allowed for subsequent progressive weaning of the enteral methadone. In contrast, the SCG which started out with a "lower" initial dose conversion ended up with higher doses of enteral methadone later on that might have resulted in over sedation and prolonged needs for intensive care dependency. However, this observation requires further prospective study in future trials.

The current study has several limitations. This was a retrospective review of patients admitted to the PICU and therefore subject to bias from incorrect or missing documentation in the patient charts. We attempted to overcome this limitation with rigorous definitions and integrity of data abstraction that we established a priori. Though it is possible that patients in the RCG happened to experience less withdrawal symptoms and were easier to wean compared to those in the SCG, both groups were well balanced with regard to age, illness severity, diagnoses, and extent of exposure to IV fentanyl infusion (Table 1). The small sample size precluded us from adjusting for confounding factors between the groups to study the independent association of methadone

Table 4 Example of dose conversion from intravenous fentanyl infusion directly to enteral methadone

A 10-kg child is receiving IV fentanyl infusion of 5 mcg/kg per hour. The total daily fentanyl dose is 5 μg/kg per hour × 24 h = 1.2 mg/d
Dose conversion ratio - methadone:fentanyl = 2.5 (rounded up from 2.3 observed in rapid conversion group in the present study that converted from IV fentanyl infusion directly to enteral methadone within 48 h) based on potency, half-life and enteral bioavailability
Total daily dose of enteral methadone = 2.5 × 1.2 mg/d = 3 mg/d administered in 2 divided doses, *i.e.*, 1.5 mg dosed every 12 h
Following the second dose of enteral methadone, the IV fentanyl infusion is decreased by 50% to 2.5 mcg/kg per hour
Following the third dose of enteral methadone, the IV fentanyl infusion is decreased again by 50% to 1.25 mcg/kg per hour
Following the fourth dose of enteral methadone, the IV fentanyl infusion is discontinued

IV: Intravenous.

dosing in relation to other clinically relevant outcomes such as ventilator free days and PICU length of stay. The findings from this study cannot be extrapolated to conversions other than from IV fentanyl infusion to enteral methadone. The dosing of enteral methadone was subject to the discretion of the attending physician and the time frame for conversion from the IV infusion, though intended to be 48 h, was variable. This study did not take into account withdrawal symptoms from discontinuation of other medications such as benzodiazepines and barbiturates. Though sedative and analgesic regimens with ketamine and dexmedetomidine could theoretically lower the risk for withdrawal[23,24], none of our patients received either of these medications. The findings of this single center study may not be generalizable to other institutions. Incomplete cross-tolerance could have also complicated assessment of our findings. This phenomenon, in which exposure to one opioid could result in some degree of tolerance with exposure to another opioid, can be partial or complete[25].

Though methadone is commonly prescribed to facilitate conversion from prolonged IV opioid infusion use and minimize opioid withdrawal in the PICU, concerns exist that methadone may be more potent than suggested when using equianalgesic dose conversion ratios from opioids such as morphine[26]. This is particularly notable as a function of prior opioid dose and tends to increase with higher doses with consequent risk for oversedation and toxicities. A recent systematic review by Johnson *et al*[27] did not find differences between weight-based and formula-based approaches to initial methadone dosing in critically ill children. However, this review did note that children receiving a formula-based approach to dosing tended to experience more instances of oversedation. The authors concluded that the most prudent course is to start with the lowest possible dose and titrate based on clinical response to avoid complications[27].

In recent years, efforts to develop pathways and protocols have emerged as rational approaches to reduce intensive care dependency and rein in healthcare costs by decreasing variations in treatment styles. Our results are similar to the findings of the quality improvement study by Abdouni *et al*[14] who observed that employing a standardized treatment protocol to convert from IV fentanyl infusion to intermittent methadone dosing using a dose conversion ratio of 2.5:1 reduced the length of opioid exposure and minimized withdrawal symptoms. By observing the feasibility of a direct conversion from IV fentanyl infusion to intermittent enteral methadone, our study provides additional support to further refine such clinical pathways and ultimately improve clinical outcomes for critically ill children.

In our institutional experience, we observed wide variation in clinician practice during conversion from IV fentanyl infusion to enteral methadone and variability in withdrawal in critically ill mechanically ventilated children exposed to prolonged sedation. In those children who converted successfully from IV fentanyl infusion to enteral methadone within a period of 48 h, a methadone:fentanyl dose conversion ratio of approximately 2.5:1 appeared to minimize withdrawal with less need for rescue opioids. Further prospective studies are needed to examine the optimum methadone:fentanyl dosing conversion to reduce withdrawal and improve clinical, economic and patient satisfaction outcomes.

COMMENTS

Background

Critically ill children are at high risk of dependence and withdrawal after prolonged intravenous (IV) opioid infusion use for sedation and analgesia which can result in considerable morbidity with prolongation of intensive care dependency. The optimal strategy to minimize such withdrawal remains controversial.

Research frontiers

Direct rapid conversion of IV opioid infusions to enteral medications are ideal to minimize withdrawal as well as enhance patient satisfaction. An additional benefit of such a strategy is to facilitate rapid transition from intensive care to home with decrease in healthcare costs.

Innovations and breakthroughs

In contrast to most previous studies that examined conversion from IV opioid infusions to IV methadone, this study demonstrates the feasibility of a direct conversion from IV fentanyl infusion to enteral methadone within a 48-h time frame with minimal withdrawal in critically ill children.

Applications

In practical terms, a direct conversion from IV fentanyl infusion to enteral methadone over a 48-h timeframe appears to be feasible in a ratio of methadone:fentanyl of 2.5:1 with minimal withdrawal and less need for rescue opioids.

Terminology

FLACC: Face, Legs, Activity, Cry and Consolability; IQR: Inter-quartile range; IV: Intravenous; LOS: Length of stay; PICU: Pediatric intensive care unit; PRISM: Pediatric Risk of Mortality; RCG: Rapid conversion group; SCG: Slow conversion group; WAT-1: Withdrawal Assessment Tool-version 1.

Peer-review

The findings are very valuable and should be shared with the scientific community. The corrections are shown as green highlight in the manuscript.

REFERENCES

1 **Anand KJ**, Arnold JH. Opioid tolerance and dependence in infants and children. *Crit Care Med* 1994; **22**: 334-342 [PMID: 8306694 DOI: 10.1097/00003246-199402000-00027]

2 **Tobias JD**. Sedation and analgesia in the pediatric intensive care unit. *Pediatr Ann* 2005; **34**: 636-645 [PMID: 16149752 DOI: 10.3928/0090-4481-20050801-12]

3 **Ista E**, van Dijk M, Gamel C, Tibboel D, de Hoog M. Withdrawal symptoms in critically ill children after long-term administration of sedatives and/or analgesics: a first evaluation. *Crit Care Med* 2008; **36**: 2427-2432 [PMID: 18596622 DOI: 10.1097/CCM.0b013e318181600d]

4 **Katz R**, Kelly HW, Hsi A. Prospective study on the occurrence of withdrawal in critically ill children who receive fentanyl by continuous infusion. *Crit Care Med* 1994; **22**: 763-767 [PMID: 8181283 DOI: 10.1097/00003246-199405000-00009]

5 **Tobias JD**, Schleien CL, Haun SE. Methadone as treatment for iatrogenic narcotic dependency in pediatric intensive care unit patients. *Crit Care Med* 1990; **18**: 1292-1293 [PMID: 1977561 DOI: 10.1097/00003246-199011000-00024]

6 **Robertson RC**, Darsey E, Fortenberry JD, Pettignano R, Hartley G. Evaluation of an opiate-weaning protocol using methadone in pediatric intensive care unit patients. *Pediatr Crit Care Med* 2000; **1**: 119-123 [PMID: 12813261 DOI: 10.1097/00130478-200010000-00005]

7 **Meyer MM**, Berens RJ. Efficacy of an enteral 10-day methadone wean to prevent opioid withdrawal in fentanyl-tolerant pediatric intensive care unit patients. *Pediatr Crit Care Med* 2001; **2**: 329-333 [PMID: 12793936 DOI: 10.1097/00130478-200110000-00009]

8 **Lugo RA**, MacLaren R, Cash J, Pribble CG, Vernon DD. Enteral methadone to expedite fentanyl discontinuation and prevent opioid abstinence syndrome in the PICU. *Pharmacotherapy* 2001; **21**: 1566-1573 [PMID: 11765307 DOI: 10.1592/phco.21.20.1566.34471]

9 **Siddappa R**, Fletcher JE, Heard AM, Kielma D, Cimino M, Heard CM. Methadone dosage for prevention of opioid withdrawal in children. *Paediatr Anaesth* 2003; **13**: 805-810 [PMID: 14617122 DOI: 10.1046/j.1460-9592.2003.01153.x]

10 **Yang F**, Tong X, McCarver DG, Hines RN, Beard DA. Population-based analysis of methadone distribution and metabolism using an age-dependent physiologically based pharmacokinetic model. *J Pharmacokinet Pharmacodyn* 2006; **33**: 485-518 [PMID: 16758333 DOI: 10.1007/s10928-006-9018-0]

11 **McCance-Katz EF**, Sullivan LE, Nallani S. Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications: a review. *Am J Addict* 2010; **19**: 4-16 [PMID: 20132117 DOI: 10.1111/j.1521-0391.2009.00005.x]

12 **Pearson EC**, Woosley RL. QT prolongation and torsades de pointes among methadone users: reports to the FDA spontaneous reporting system. *Pharmacoepidemiol Drug Saf* 2005; **14**: 747-753 [PMID: 15918160 DOI: 10.1002/pds.1112]

13 **Tobias JD**. Tolerance, withdrawal, and physical dependency after long-term sedation and analgesia of children in the pediatric intensive care unit. *Crit Care Med* 2000; **28**: 2122-2132 [PMID: 10890677 DOI: 10.1097/00003246-200006000-00079]

14 **Abdouni R**, Reyburn-Orne T, Youssef TH, Haddad IY, Gerkin RD. Impact of a Standardized Treatment Guideline for Pediatric Iatrogenic Opioid Dependence: A Quality Improvement Initiative. *J Pediatr Pharmacol Ther* 2016; **21**: 54-65 [PMID: 26997929 DOI: 10.5863/1551-6776-21.1.54]

15 **Bowens CD**, Thompson JA, Thompson MT, Breitzka RL, Thompson DG, Sheeran PW. A trial of methadone tapering schedules in pediatric intensive care unit patients exposed to prolonged sedative infusions. *Pediatr Crit Care Med* 2011; **12**: 504-511 [PMID: 21076361 DOI: 10.1097/PCC.0b013e3181fe38f5]

16 **Shaheen PE**, Walsh D, Lasheen W, Davis MP, Lagman RL. Opioid equianalgesic tables: are they all equally dangerous? *J Pain Symptom Manage* 2009; **38**: 409-417 [PMID: 19735901 DOI: 10.1016/j.jpainsymman.2009.06.004]

17 **Pollack MM**, Patel KM, Ruttimann UE. PRISM III: an updated Pediatric Risk of Mortality score. *Crit Care Med* 1996; **24**: 743-752 [PMID: 8706448 DOI: 10.1097/00003246-199605000-00004]

18 **Franck LS**, Harris SK, Soetenga DJ, Amling JK, Curley MA. The Withdrawal Assessment Tool-1 (WAT-1): an assessment instrument for monitoring opioid and benzodiazepine withdrawal symptoms in pediatric patients. *Pediatr Crit Care Med* 2008; **9**: 573-580 [PMID: 18838937 DOI: 10.1097/PCC.0b013e31818c8328]

19 **Merkel S**, Voepel-Lewis T, Malviya S. Pain assessment in infants and young children: the FLACC scale. *Am J Nurs* 2002; **102**: 55-58 [PMID: 12394307 DOI: 10.1097/00000446-200210000-00024]

20 **Solodiuk J**, Curley MA. Pain assessment in nonverbal children with severe cognitive impairments: the Individualized Numeric Rating Scale (INRS). *J Pediatr Nurs* 2003; **18**: 295-299 [PMID: 12923744 DOI: 10.1016/S0882-5963(03)00090-3]

21 **Wong DL**, Baker CM. Smiling faces as anchor for pain intensity scales. *Pain* 2001; **89**: 295-300 [PMID: 11291631 DOI: 10.1016/S0304-3959(00)00375-4]

22 **Tobias JD**, Deshpande JK, Gregory DF. Outpatient therapy of iatrogenic drug dependency following prolonged sedation in the pediatric intensive care unit. *Intensive Care Med* 1994; **20**: 504-507 [PMID: 7995868 DOI: 10.1007/BF01711905]

23 **Anand KJ**, Willson DF, Berger J, Harrison R, Meert KL, Zimmerman J, Carcillo J, Newth CJ, Prodhan P, Dean JM, Nicholson C. Tolerance and withdrawal from prolonged opioid use in critically ill children. *Pediatrics* 2010; **125**: e1208-e1225 [PMID: 20403936 DOI: 10.1542/peds.2009-0489]

24 **Golding CL**, Miller JL, Gessouroun MR, Johnson PN. Ketamine Continuous Infusions in Critically Ill Infants and Children. *Ann Pharmacother* 2016; **50**: 234-241 [PMID: 26783355 DOI: 10.1177/1060028015626932]

25 **Choe CH**, Smith FL. Sedative tolerance accompanies tolerance to the analgesic effects of fentanyl in infant rats. *Pediatr Res* 2000; **47**: 727-735 [PMID: 10832729 DOI: 10.1203/00006450-200006000-00008]

26 **Lawlor PG**, Turner KS, Hanson J, Bruera ED. Dose ratio between morphine and methadone in patients with cancer pain: a retrospective study. *Cancer* 1998; **82**: 1167-1173 [PMID: 9506365 DOI: 10.1002/(SICI)1097-0142(19980315)82:6<1167::AID-CNCR23>3.0.CO;2-3]

27 **Johnson PN**, Boyles KA, Miller JL. Selection of the initial methadone regimen for the management of iatrogenic opioid abstinence syndrome in critically ill children. *Pharmacotherapy* 2012; **32**: 148-157 [PMID: 22392424 DOI: 10.1002/PHAR.1001]

P- Reviewer: Krishnan T, Sangkhathat S **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Li D

World Journal of Clinical Pediatrics

Submit a Manuscript: http://www.f6publishing.com

World J Clin Pediatr 2017 May 8; 6(2): 118-123

DOI: 10.5409/wjcp.v6.i2.118

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Retrospective Study

Significance of platelet count in children admitted with bronchiolitis

Amar Al Shibli, Najla Alkuwaiti, May Hamie, Dima Abukhater, Muhammad B Noureddin, Abdulla Amri, Salwa Al Kaabi, Aysha Al Kaabi, Mariam Harbi, Hassib Narchi

Amar Al Shibli, Najla Alkuwaiti, May Hamie, Dima Abukhater, Muhammad B Noureddin, Abdulla Amri, Salwa Al Kaabi, Aysha Al Kaabi, Mariam Harbi, Department of Pediatrics, Tawam Hospital, PO Box 15258, Al Ain, United Arab Emirates

Hassib Narchi, Department of Pediatrics, College of Medicine and Health Sciences, United Arab Emirates University, PO Box 17666, Al Ain, United Arab Emirates

Author contributions: Al Shibli A designed the research, coordinated and supervised data collection, co-wrote and supervised the report; Narchi H designed the study, the data collection instruments, carried out the analyses and co-wrote the manuscript; Hamie M, Abukhater D, Noureddin MB, Al Kaabi S, Al Kaabi A, Alkuwaiti N and Al Harbi M collected the data, reviewed and revised the manuscript, and approved the final manuscript as submitted; all authors have approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Institutional review board statement: Institutional Review Board (IRB 296/13) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The requirement for consent was waived as it was a retrospective study and patient anonymity was preserved.

Informed consent statement: As this was a retrospective review of case notes where all the clinical data was anonymized, patients were not required to give informed consent to the study.

Conflict-of-interest statement: The authors have no financial relationships to disclose.

Data sharing statement: No additional data are available.

Manuscript source: Unsolicited manuscript

Correspondence to: Amar Al Shibli, FRCPCH, Department of Pediatrics, Tawam Hospital, PO Box 15258, Al Ain, United Arab Emirates. ashibli@seha.ae
Telephone: +971-3-7677444

Received: April 27, 2016
Peer-review started: May 3, 2016
First decision: July 27, 2016
Revised: October 23, 2016
Accepted: November 21, 2016
Article in press: November 22, 2016
Published online: May 8, 2017

Abstract

AIM

To determine the true prevalence of thrombocytosis in children less than 2 years of age with bronchiolitis, its association with risk factors, disease severity and thromboembolic complications.

METHODS

A retrospective observational medical chart review of 305 infants aged two years or less hospitalized for bronchiolitis. Clinical outcomes included disease severity, duration of hospital stay, admission to pediatric intensive care unit, or death. They also included complications of thrombocytosis, including thromboembolic complications such as cerebrovascular accident, acute coronary syndrome, deep venous thrombosis, pulmonary embolus, mesenteric thrombosis and arterial thrombosis and also hemorrhagic complications such as bleeding (spontaneous hemorrhage in the skin, mucous membranes, gastrointestinal, respiratory, or genitourinary tracts).

RESULTS

The median age was 4.7 mo and 179 were males (59%). Respiratory syncytial virus was isolated in 268 (84%), adenovirus in 23 (7%) and influenza virus A or B in 13 (4%). Thrombocytosis (platelet count > 500 × 10^9/L) occurred in 88 (29%; 95%CI: 24%-34%), more commonly in younger infants with the platelet count declining with age. There was no significant association with the duration of illness, temperature on admission, white blood cell count, serum C-reactive protein concentration, length of hospital stay or admission to the intensive care unit. No death, thrombotic or hemorrhagic events occurred.

CONCLUSION

Thrombocytosis is common in children under two years of age admitted with bronchiolitis. It is not associated with disease severity or thromboembolic complications.

Key words: Hospitalization; Bronchiolitis; Platelet count; Thrombocytosis; Infant; Virus diseases

Core tip: This is as a retrospective observational study of platelet counts in 305 infants aged two years or less who were hospitalized for bronchiolitis. Thrombocytosis (platelet count > 500 × 10^9/L) was frequent, occurring in 88 (29%; 95%CI: 24%-34%), more commonly in younger infants with the platelet count declining with age. There was no significant association with the duration of illness, temperature on admission, white blood cell count, serum C-reactive protein concentration, length of hospital stay, admission to the intensive care unit, death, thrombotic or hemorrhagic complications.

Al Shibli A, Alkuwaiti N, Hamie M, Abukhater D, Noureddin MB, Amri A, Al Kaabi S, Al Kaabi A, Harbi M, Narchi H. Significance of platelet count in children admitted with bronchiolitis. *World J Clin Pediatr* 2017; 6(2): 118-123 Available from: URL: http://www.wjgnet.com/2219-2808/full/v6/i2/118.htm DOI: http://dx.doi.org/10.5409/wjcp.v6.i2.118

INTRODUCTION

Bronchiolitis is a common viral infection in young children, usually caused by respiratory syncytial virus (RSV), adenovirus infections or influenza. Thrombocytosis is uncommon and its incidence and etiology are age-dependent[1]. It is rare in childhood, especially the primary form, which is of hemopoietic nature. More common is the secondary form or reactive thrombocytosis, which is often asymptomatic, transient, occurring during the course of a viral infectious illness, mainly respiratory, and it is often considered to be an acute phase reactant response to cytokines production during the infection. Other causes of reactive thrombocytosis include inflammation, anemia, hypoxia and some medications[2-6]. Cytokines [interleukins (IL)-6, IL-8, IL-11] and thrombopoietin have been implicated it its pathogenesis[7,8].

Thrombocytosis has only occasionally been reported in viral bronchiolitis with a prevalence ranging from as low as 8.4% up to 38.6%, with higher platelet counts observed in RSV positive infections[9,10]. This has led to the suggestion that RSV infection should strongly be suspected when thrombocytosis occurs in a child with a respiratory infection[11,12]. Although platelets play an important role in anti-microbial host defense, in the induction of inflammation and tissue repair, the significance of thrombocytosis during an infection is not fully clarified, as it may be caused by both disease aggressiveness and a higher capacity for host defense. For example, in adult patients hospitalized for community- acquired pneumonia, a high platelet count, is associated with a significant increase risk of mortality[13]. Likewise, in children with human immunodeficiency virus infection, thrombocytosis correlates with severe disease[14].

Reactive thrombocytosis in children is usually benign and does not cause thromboembolic or hemorrhagic complications, except if it occurs secondary to splenectomy or if there is underlying disease with additional thrombotic risk factors such as thalassemia[15,16] especially when complicated by cardiomyopathy, diabetes, hepatopathy and portal hypertension[17]. Neonatal thrombocytosis carries a higher thrombo-embolic risk in the presence of risk factors like maternal diabetes and antiphospholipid syndrome, septicemia, intrauterine growth retardation or in the presence of cyanotic cardiac malformation[18].

None of the few reports of thrombocytosis in children with bronchiolitis has looked at its association with risk factors, disease severity or thromboembolic complications. We therefore undertook this study to ascertain the prevalence of thrombocytosis in a cohort of children with bronchiolitis admitted to a general pediatric ward and analyze the risk factors associated with it. We also looked for thromboembolic complications and analyzed if elevated platelet count was associated with, and therefore a marker of bronchiolitis severity.

MATERIALS AND METHODS

The study was a retrospective observational medical chart review of all infants aged two years or less who were hospitalized for bronchiolitis in the pediatric departments of Tawam hospital from 1st November 2008 to 30th June 2012. Indications for admission included worsening of the respiratory status, decreased oral intake, requirement for oxygen or parenteral therapy. The diagnosis of bronchiolitis was clinical and was made by the physician on admission based on the presence of an upper respiratory tract infection (either by history or by cough or rhinorrhea on physical examination), tachypnea, hypoxia, cough, subcostal or intercostal retractions, nasal flaring, grunting, with wheezing and/or crackles on auscultation. The management of admitted children was

left to the discretion of the attending physician.

Excluded from the study were children with a bacterial co-infection, chronic disease, immune deficiencies, splenectomy, congenital cyanotic heart disease with polycythemia, presence of intravascular lines, treatment with medications associated with thrombocytosis, or with a personal or family history of thrombophilia.

Data for each infant were extracted through review of emergency department case files and admission notes. Demographic data (gender, age, weight at birth, and gestational age), duration of illness before admission and clinical features at the time of admission including basic observations were recorded. Maximal temperature was defined as the highest rectal temperature recorded in the emergency department or at the time of admission to the pediatric department and fever was defined as a temperature > 38 ℃. Nasopharyngeal aspirates were obtained on admission and sent for enzyme-linked immunoassay rapid antigen detection of RSV (Tru RSV®, Meridian Bioscience, INC), and adenovirus, influenza A and B, parainfluenza 1, 2 and 3 viruses (LIGHT DIAGNOSTICS™ SimulFluor® Respiratory Screen, EMD Millipore). Platelet count was measured by CELL - DYN Sapphire (Abbot). Thrombocytosis was defined as a platelet count of more than 500 × 10^9/L. Counts of > 500 and ⩽ 700 × 10^9/L were considered mild thrombocytosis, levels of > 700 and ⩽ 900 × 10^9/L as moderate thrombocytosis, and levels of > 900 × 10^9/L as severe thrombocytosis[9]. For the purpose of the study only the first platelet count taken upon admission was used. Serum C-reactive protein (CRP) was measured with the Beckman Coulter DXB-800, with values < 8 mg/L defined as normal.

Clinical outcomes included disease severity as judged by duration of hospital stay, admission to pediatric intensive care unit (PICU), or death. They also included complications of thrombocytosis, including thromboembolic complications such as cerebrovascular accident, acute coronary syndrome, deep venous thrombosis, pulmonary embolus, mesenteric thrombosis and arterial thrombosis[19-21] and also hemorrhagic complications such as bleeding (spontaneous hemorrhage in the skin, mucous membranes, gastrointestinal, respiratory, or genitourinary tracts).

Statistical analysis

The prevalence of thrombocytosis was calculated with 95% confidence intervals (CI). Proportions were compared with the χ^2 test, or the Fisher exact test if the number of observations was less than 5. The Student *t*-test was used to compare the means of Normally distributed variables between two groups. Analysis of variance was used to compare the means of normally distributed continuous variables amongst more than 2 groups, with Bonferroni adjustment for multiple comparisons. The odds and odds ratio of the association of thrombocytosis with the type and number of isolated viruses were calculated with 95%CI. For all statistical analyses, a 2-tailed *P* value was considered statistically significant if < 0.05.

Ethical approval

Approval was granted by the Institutional Review Board (IRB 296/13) and the requirement for consent was waived as it was a retrospective study and patient anonymity was preserved.

RESULTS

Descriptive

During the study period there were 305 children admitted for acute bronchiolitis (*n* = 179 males, 59%). Their median age was 4.7 mo (mean ± SD 6.5 ± 0.2 mo, range 7 d to 1.9 years) and 49 (18%) were born preterm (< 38 completed weeks of gestation) with a median gestational age 40 of weeks (mean 39, range 23 to 42 wk) and a median birth weight of 3000 g (median 2.9, range 870 to 4600 g). The median duration of symptoms prior to admission was three days (mean ± SD 2.8 ± 1.2, range 0 to 6 d) and 203 children (68%) were febrile on presentation. Mild to moderate dehydration was present in 131 children (43%).

Virology studies were performed on all. Infection with a single virus occurred in 291 children (95%). RSV was isolated in 255 children (84%), adenovirus in 23 (7%) and influenza virus A or B in 13 (4%). Co-infection of RSV infection with adenovirus occurred in 8 (3%) and with influenza in six (2%).

The mean ± SD platelet count was 431 ± 141 × 10^9/L (median 421 × 10^9/L and range 51 to 1000 × 10^9/L). The platelet count was normal in 213 children (70%). Thrombocytosis occurred in 88 children (prevalence 29%; 95%CI 24% to 34%) and it was mild in 78 children (89%), moderate in 9 (10%) and severe in one (1%). The mean ± SD of blood white cell count were 3.4 ± 1.0 × 10^9/L and for serum CRP 1.4 ± 1.2 mg/L.

Forty children (1.3%) required admission to PICU: 25 (63%) required continuous positive airway pressure, mechanical ventilation was required in nine (22%) and six children (15%) only required additional oxygen administration. No death occurred. The mean ± SD duration of hospital stay was 4.2 ± 5.2 d (median 3, range 1 to 54 d). No thrombotic or hemorrhagic events were observed and no treatment for thrombocytosis was initiated for any of the affected children.

Analysis

Thrombocytosis occurred significantly more commonly in younger infants (mean age 4.8 mo) (Table 1). The platelet level significantly declined with advancing age (Figure 1) with a slope of -8.9 in a linear regression model ($P < 0.001$) resulting in a decrease of approximately 9 × 10^9/L in the platelet count for each month of increase in age.

There was no significant difference in platelet count between genders, history of prematurity, duration of illness prior to admission, temperature on admission,

Table 1 Characteristics of 305 children admitted with bronchiolitis

	Platelet count ($\times 10^9$/L) *n* (%) or mean ± SD		*P* value
	> 500	< 500	
Children	217 (71)	88 (29)	
Age (mo)	7.3 ± 5.8	4.8 ± 4.1	< 0.001[1]
Males	132 (74)	47 (26)	0.2[2]
Born < 38 wk gestation	32 (65)	17 (35)	0.3[2]
Duration of illness before admission (d)	2.9 ± 1.2	2.7 ± 1.4	0.3[1]
Fever (> 38 ℃) on admission	148 (73)	55 (27)	0.3[2]
Blood white cell count ($\times 10^9$/L)	3.5 ± 1.1	3.2 ± 0.5	0.8[1]
Nasopharyngeal aspirate isolate			
RSV	189 (74)	66 (26)	
Adenovirus	13 (57)	10 (43)	
Influenza	6 (46)	7 (54)	0.09
RSV + Adenovirus	5 (62)	3 (38)	
RSV + Influenza	3 (50)	3 (50)	
Serum CRP (mg/L)	1.4 ± 1.3	1.5 ± 1.2	0.5[1]
Duration of hospitalization (d)	4 ± 5.5	4.4 ± 4.2	0.6[1]
Admitted to intensive care	25 (62)	15 (37)	0.2[2]

[1]*t*-test; [2]χ^2 test or Fisher exact test if number < 5. *n*: Number of infants; SD: Standard deviation; RSV: Respiratory syncytial virus; CRP: C-reactive protein.

Table 2 Thrombocytosis (platelet count > 500 × 10^9/L) and number of pathogenic viruses identified on nasopharyngeal aspirates of 305 children with bronchiolitis

No. of virus isolated	Total	Thrombocytosis *n* (%)	Odds	OR (95%CI)	*P* value
One	291	82 (28)	0.4	1.0 (reference)	0.2
Two	14	6 (43)	0.75	1.9 (0.6-5.7)	

n: Number of infants; OR: Odds ratio; CI: Confidence intervals.

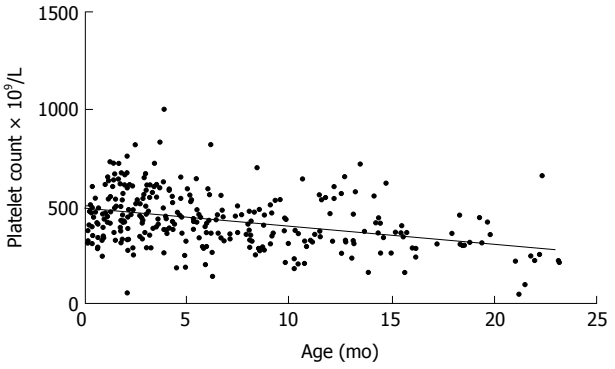


Figure 1 Platelet count by age in 305 children admitted with bronchiolitis. Linear regression coefficient = -8.9 (*P* < 0.001).

blood white blood cell count or serum CRP concentration (Table 1). No association with dehydration was observed (*P* = 0.06). The severity of thrombocytosis was not significantly associated with disease severity as judged by length of hospital stay or admission to the pediatric intensive care unit (Table 2).

There was no significant difference in platelet count amongst the viruses identified in nasopharyngeal aspirates (Table 1), nor between infection with a single or more viruses (Table 3). Similarly, no significant difference in the prevalence of thrombocytosis (*P* = 0.5) was found between the children with RSV-positive infection (39%) and all those who were RSV-negative (41%).

DISCUSSION

The prevalence of thrombocytosis in children under the age of two years admitted for bronchiolitis was 29% (95%CI: 24%-34%). This contrasts sharply with a reported prevalence of 8% in a previous report[11]. The reason might be that the previous study included all respiratory infections, including measles infection, and not only bronchiolitis. In addition, as older children (up to nine years) were enrolled in that review, the lower prevalence of thrombocytosis is not surprising because it occurs less commonly in older children[1,22,23]. Another study reported a much higher prevalence (38%) of thrombocytosis in infants with bronchiolitis, but it enrolled only infants younger than four months where thrombocytosis is more prevalent[12]. We confirms the findings of previous reports that thrombocytosis in children with bronchiolitis is more common in the very young and declines steadily with age[22,23].

Although it is known that reactive thrombocytosis during childhood infections peaks during the second week of the illness[24], we deliberately chose to examine the platelet count on admission because the great majority of children with bronchiolitis are likely to be asymptomatic or discharged from hospital during the second week of the infection. We found no association of thrombocytosis with the duration of illness prior to admission, perhaps because platelet counts are often higher in patients with long duration of illness prior to admission[4] and children are usually admitted early in the course of bronchiolitis. We acknowledge, however, that firm conclusions regarding the timing of thrombocytosis in bronchiolitis cannot be drawn because only one platelet value was recorded in each patient and there were no serial measurements. Our findings corroborate previous reports, which showed that the secondary thrombocytosis is common and occurs early in RSV infection[11].

In our study, thrombocytosis occurred less commonly in RSV infections compared to other viruses. This contrasts with the results of a previous study which found it more common in RSV infections and even suggested that thrombocytosis should be considered as an early laboratory marker of RSV infection in childhood; however it included not only bronchiolitis, but all types of respiratory infections, including measles, and also enrolled much older children, up to 9 years of age[11,15]. Another report found a higher prevalence of thrombocytosis in RSV positive compared to RSV negative infections; however, the enrolled children were much younger, under four months of age, and no comparison with other viruses was performed[12]. Another possible explanation for the different results obtained in our study is that, unlike viral

Table 3 Degree of thrombocytosis and outcomes in 305 children with bronchiolitis

	Thrombocytosis, *n* (%)				*P* value
	None (*n* = 217)	Mild (*n* = 78)	Moderate (*n* = 9)	Severe (*n* = 1)	
Mean (SD) duration of hospitalization in days	4.0 (5.5)	4.4 (4)	4.5 (3)	5.0 (0)	0.9[1]
Admission to ICU	25 (11)	25 (30)	3 (33)	0 (0)	0.2[2]

[1]ANOVA with Bonferroni correction for multiple comparisons; [2]Fisher exact test. *n*: Number of infants; Thrombocytosis: None if platelet level < 500 × 10^9/L; mild if 500 to 700 × 10^9/L; moderate if 700 to ⩽ 900 × 10^9/L and severe if > 900 × 10^9/L. ICU: Intensive care unit.

culture and polymerase chain reaction, the rapid antigen detection method that we have used does not have high sensitivity for the detection of viruses other than RSV and influenza.

Unlike earlier reports, thrombocytosis on admission was not associated with the severity of inflammation which we defined as the presence of fever, leukocytosis or elevated serum CRP level. It has already been established that, in the first week of acute infections, serum CRP, IL-6 and thrombopoeitin levels start to rise while the platelet count is still normal. The platelet count peaks later, in the second and third weeks when CRP and IL-6 levels are decreasing[8]. This, however, does not explain our findings because all admissions for bronchiolitis occurred within one week of the onset of symptoms, when fever and serum CRP are expected to be still elevated and the platelet count have not yet started to rise. The exact explanation for that discrepancy remains therefore elusive.

We did not find that disease severity, as defined by length of hospital stay or admission to the intensive care unit, was associated with the presence of thrombocytosis nor its severity. This is in contrast with a previous report that found thrombocytosis to predict mortality, but the cause for the difference is likely to be that, unlike our study in children with viral bronchiolitis, it had enrolled elderly adults with community-acquired pneumonia presumably of bacterial origin[19].

The absence of thromboembolic or hemorrhagic complications observed in our study confirms previous reports of reactive thrombocytosis[25,26]. In accordance with published guidelines, no treatment for thrombocytosis was initiated for any of the children in this study as none had intravascular lines, or congenital cyanotic heart disease associated with thrombosis, or medications associated with thrombocytosis, or a personal or a family history of thrombophilia[3,27].

The study has some limitations. The bronchiolitis score was not used as an index of disease severity, nor was the platelet count measured serially throughout the stay in hospital. Similarly, cytokines and thrombopoietin measurements were not performed. These limitations should be addressed in future studies.

In conclusion, secondary thrombocytosis is common in children under two years of age admitted with bronchiolitis, affecting 29% of them. It is not associated with a severe course for bronchiolitis or with thromboembolic complications.

COMMENTS

Background

Bronchiolitis is a common viral infection in young children, usually caused by respiratory syncytial virus (RSV), influenza or adenovirus infections. Secondary or reactive thrombocytosis may occur and is considered to be an acute phase reactant response to thrombopoietin or cytokines production during the infection [interleukins (IL)-6, IL-8, IL-11]. Its prevalence in bronchiolitis may range from 8.4% to 38.6%, with higher platelet counts observed in RSV positive infections. It usually does not result in thromboembolic or hemorrhagic complications.

Research frontiers

None of the few reports of thrombocytosis in children with bronchiolitis has looked at its association with risk factors, disease severity or thromboembolic complications. The authors therefore undertook this study to ascertain the prevalence of thrombocytosis in a cohort of children with bronchiolitis admitted to a general pediatric ward and analyze the risk factors associated with it. They also looked for thromboembolic complications and analyzed if elevated platelet count was associated with, and therefore a marker of bronchiolitis severity.

Innovations and breakthroughs

In this retrospective observational study of platelet counts in 305 infants aged two years or less who were hospitalized for bronchiolitis, thrombocytosis (platelet count > 500 × 10^9/L) was frequent, occurring in 88 (29%; 95%CI: 24%-34%), more commonly in younger infants with the platelet count declining with age. There was no significant association with the duration of illness, temperature on admission, white blood cell count, serum C-reactive protein concentration, length of hospital stay, admission to the intensive care unit, death, thrombotic or hemorrhagic complications.

Applications

Thrombocytosis is common in children under two years of age admitted with bronchiolitis. It is not associated with disease severity or thromboembolic complications.

Terminology

Thrombocytosis is defined as a platelet count of more than 500 × 10^9/L. Counts of > 500 and ⩽ 700 × 10^9/L are considered mild thrombocytosis, levels of > 700 and ⩽ 900 × 10^9/L as moderate thrombocytosis, and levels of > 900 × 10^9/L as severe thrombocytosis.

Peer-review

The article is well written and interesting.

REFERENCES

1 **Matsubara K**, Fukaya T, Nigami H, Harigaya H, Hirata T, Nozaki H, Baba K. Age-dependent changes in the incidence and etiology of childhood thrombocytosis. *Acta Haematol* 2004; **111**: 132-137 [PMID: 15034233 DOI: 10.1159/000076520]

2 **Dame C**, Sutor AH. Primary and secondary thrombocytosis in childhood. *Br J Haematol* 2005; **129**: 165-177 [PMID: 15813844 DOI: 10.1111/j.1365-2141.2004.05329.x]

3 **Harrison CN**, Bareford D, Butt N, Campbell P, Conneally E, Drummond M, Erber W, Everington T, Green AR, Hall GW,

Hunt BJ, Ludlam CA, Murrin R, Nelson-Piercy C, Radia DH, Reilly JT, Van der Walt J, Wilkins B, McMullin MF. Guideline for investigation and management of adults and children presenting with a thrombocytosis. *Br J Haematol* 2010; **149**: 352-375 [PMID: 20331456 DOI: 10.1111/j.1365-2141.2010.08122.x]

4 **Mantadakis E**, Tsalkidis A, Chatzimichael A. Thrombocytosis in childhood. *Indian Pediatr* 2008; **45**: 669-677 [PMID: 18723910]

5 **Schafer AI**. Thrombocytosis. *N Engl J Med* 2004; **350**: 1211-1219 [PMID: 15028825 DOI: 10.1056/NEJMra035363]

6 **Sutor AH**. Thrombocytosis in childhood. *Semin Thromb Hemost* 1995; **21**: 330-339 [PMID: 8588160 DOI: 10.1055/s-2007-1000654]

7 **Matsubara K**, Baba K, Nigami H, Harigaya H, Ishiguro A, Kato T, Miyazaki H. Early elevation of serum thrombopoietin levels and subsequent thrombocytosis in healthy preterm infants. *Br J Haematol* 2001; **115**: 963-968 [PMID: 11843834 DOI: 10.1046/j.1365-2141.2001.03183.x]

8 **Ishiguro A**, Suzuki Y, Mito M, Shimbo T, Matsubara K, Kato T, Miyazaki H. Elevation of serum thrombopoietin precedes thrombocytosis in acute infections. *Br J Haematol* 2002; **116**: 612-618 [PMID: 11849220 DOI: 10.1046/j.0007-1048.2001.03304.x]

9 **Akaboshi I**, Fugita K, Abe A, Tanaka T. An unusual case of thrombocytosis associated with concurrent cytomegalovirus and respiratory syncytial virus infection in an immunocompetent infant: possible roles of thrombopoietin and interleukin-6. *J Infect* 2005; **51**: e97-100 [PMID: 16230213 DOI: 10.1016/j.jinf.2004.09.014]

10 **Mammas I**, Koutsaftiki C, Tapaki-Papadopoulou G, Myriokefalitakis N. Respiratory syncytial virus (RSV) bronchiolitis and excessive thrombocytosis. *Acta Paediatr* 2010; **99**: 489-490 [PMID: 20064137 DOI: 10.1111/j.1651-2227.2009.01671.x]

11 **Kubota M**, Maeda H, Yoshimoto J, Kobayashi K, Usami I, Yamaoka K. Thrombocytosis at an early stage of respiratory tract viral infection. *Acta Paediatr* 2005; **94**: 364-366 [PMID: 16028657]

12 **Bilavsky E**, Yarden-Bilavsky H, Shouval DS, Fisch N, Garty BZ, Ashkenazi S, Amir J. Respiratory syncytial virus-positive bronchiolitis in hospitalized infants is associated with thrombocytosis. *Isr Med Assoc J* 2010; **12**: 39-41 [PMID: 20450128]

13 **Mirsaeidi M**, Peyrani P, Aliberti S, Filardo G, Bordon J, Blasi F, Ramirez JA. Thrombocytopenia and thrombocytosis at time of hospitalization predict mortality in patients with community-acquired pneumonia. *Chest* 2010; **137**: 416-420 [PMID: 19837825 DOI: 10.1378/chest.09-0998]

14 **Ellaurie M**. Thrombocytosis in pediatric HIV infection. *Clin Pediatr* (Phila) 2004; **43**: 627-629 [PMID: 15378149 DOI: 10.1177/000992280404300707]

15 **Shebl SS**, el-Sharkawy HM, el-Fadaly NH. Haemostatic disorders in nonsplenectomized and splenectomized thalassaemic children. *East Mediterr Health J* 1999; **5**: 1171-1177 [PMID: 11924107]

16 **Sutor AH**. Screening children with thrombosis for thrombophilic proteins. Cui bono? *J Thromb Haemost* 2003; **1**: 886-888 [PMID: 12871352 DOI: 10.1046/j.1538-7836.2003.00159.x]

17 **Borgna Pignatti C**, Carnelli V, Caruso V, Dore F, De Mattia D, Di Palma A, Di Gregorio F, Romeo MA, Longhi R, Mangiagli A, Melevendi C, Pizzarelli G, Musumeci S. Thromboembolic events in beta thalassemia major: an Italian multicenter study. *Acta Haematol* 1998; **99**: 76-79 [PMID: 9554453]

18 **Edstrom CS**, Christensen RD. Evaluation and treatment of thrombosis in the neonatal intensive care unit. *Clin Perinatol* 2000; **27**: 623-641 [PMID: 10986632 DOI: 10.1016/S0095-5108(05)70042-7]

19 **Harrison CN**, Gale RE, Machin SJ, Linch DC. A large proportion of patients with a diagnosis of essential thrombocythemia do not have a clonal disorder and may be at lower risk of thrombotic complications. *Blood* 1999; **93**: 417-424 [PMID: 9885203]

20 **Pearson TC**. The risk of thrombosis in essential thrombocythemia and polycythemia vera. *Semin Oncol* 2002; **29**: 16-21 [PMID: 12096353]

21 **Vannucchi AM**, Barbui T. Thrombocytosis and thrombosis. *Hematology Am Soc Hematol Educ Program* 2007: 363-370 [PMID: 18024652 DOI: 10.1182/asheducation-2007.1.363]

22 **Vora AJ**, Lilleyman JS. Secondary thrombocytosis. *Arch Dis Child* 1993; **68**: 88-90 [PMID: 8435017 DOI: 10.1136/adc.68.1.88]

23 **Yohannan MD**, Higgy KE, al-Mashhadani SA, Santhosh-Kumar CR. Thrombocytosis. Etiologic analysis of 663 patients. *Clin Pediatr* (Phila) 1994; **33**: 340-343 [PMID: 8200167 DOI: 10.1177/000992289403300605]

24 **Cecinati V**, Brescia L, Esposito S. Thrombocytosis and infections in childhood. *Pediatr Infect Dis J* 2012; **31**: 80-81 [PMID: 22217969 DOI: 10.1097/INF.0b013e318241f47a]

25 **Chan KW**, Kaikov Y, Wadsworth LD. Thrombocytosis in childhood: a survey of 94 patients. *Pediatrics* 1989; **84**: 1064-1067 [PMID: 2587135]

26 **Griesshammer M**, Bangerter M, Sauer T, Wennauer R, Bergmann L, Heimpel H. Aetiology and clinical significance of thrombocytosis: analysis of 732 patients with an elevated platelet count. *J Intern Med* 1999; **245**: 295-300 [PMID: 10205592 DOI: 10.1046/j.1365-2796.1999.00452.x]

27 **Denton A**, Davis P. Extreme thrombocytosis in admissions to paediatric intensive care: no requirement for treatment. *Arch Dis Child* 2007; **92**: 515-516 [PMID: 17515621 DOI: 10.1136/adc.2006.111484]

P- Reviewer: Urganci N, Trovato GM **S- Editor**: Kong JX
L- Editor: A **E- Editor**: Li D

World Journal of Clinical Pediatrics

Submit a Manuscript: http://www.f6publishing.com

World J Clin Pediatr 2017 May 8; 6(2): 124-131

DOI: 10.5409/wjcp.v6.i2.124

ISSN 2219-2808 (online)

ORIGINAL ARTICLE

Observational Study

Decision-making patterns in managing children with suspected biliary dyskinesia

Warapan Nakayuenyongsuk, Hassan Choudry, Karla Au Yeung, Wikrom Karnsakul

Warapan Nakayuenyongsuk, Lucile Packard Children's Hospital, Stanford University School of Medicine, Palo Alto, CA 94305, United States

Hassan Choudry, Karla Au Yeung, Wikrom Karnsakul, Pediatric Liver Center, Johns Hopkins University School of Medicine, Baltimore, MD 21287, United States

Institutional review board statement: The study was reviewed and approved by Institutional review board statement of Johns Hopkins University School of Medicine.

Conflict-of-interest statement: No potential conflicts of interest relevant to this article were reported.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

Correspondence to: Wikrom Karnsakul, MD, Associate Professor, Pediatric Liver Center, Johns Hopkins University School of Medicine, CMSC-2 600 North Wolfe Street, Baltimore, MD 21287, United States. wkarnsa1@jhmi.edu
Telephone: +1-410-9558769
Fax: +1-410-9551464

Received: September 19, 2016
Peer-review started: September 20, 2016
First decision: October 28, 2016
Revised: December 4, 2016
Accepted: January 11, 2017
Article in press: January 14, 2017
Published online: May 8, 2017

Abstract

AIM

To explore and to analyze the patterns in decision-making by pediatric gastroenterologists in managing a child with a suspected diagnosis of functional gallbladder disorder (FGBD).

METHODS

The questionnaire survey included a case history with right upper quadrant pain and was sent to pediatric gastroenterologists worldwide *via* an internet list server called the PEDGI Bulletin Board.

RESULTS

Differences in decision-making among respondents in managing this case were observed at each level of investigations and management. Cholecystokinin-scintigraphy scan (CCK-CS) was the most common investigation followed by an endoscopy. A proton pump inhibitor was most commonly prescribed treating the condition. The majority of respondents considered a referral for a surgical evaluation when CCK-CS showed a decreased gallbladder ejection fraction (GBEF) value with biliary-type pain during CCK injection.

CONCLUSION

CCK infusion rate in CCK-CS-CS and GBEF cut-off limits were inconsistent throughout practices. The criteria for a referral to a surgeon were not uniform from one practitioner to another. A multidisciplinary team approach with pediatric gastroenterologists and surgeons is required guide the decision-making managing a child with suspected FGBD.

Key words: Biliary dyskinesia; Functional gallbladder disorder; Cholecystectomy; Gallbladder ejection fraction

Core tip: Functional gallbladder disorder (FGBD) is a common motility disorder of the gallbladder that results in abdominal pain and cholecystectomy in children. The guideline for managing children with FGBD is lacking. The questionnaire survey is a pilot study performed by pediatric gastroenterologists worldwide *via* the PEDGI Bulletin Board. Differences in decision-making among respondents in managing this case were observed at each level of investigations and management. Since, a different risk-benefit ratio should be considered in children with suspected FGBD. The authors include an algorithm for the approach in managing children with suspected FGBD based on literature review.

Nakayuenyongsuk W, Choudry H, Yeung KA, Karnsakul W. Decision-making patterns in managing children with suspected biliary dyskinesia. *World J Clin Pediatr* 2017; 6(2): 124-131 Available from: URL: http://www.wjgnet.com/2219-2808/full/v6/i2/124.htm DOI: http://dx.doi.org/10.5409/wjcp.v6.i2.124

INTRODUCTION

Functional gallbladder disorder (FGBD) is a motility disorder of the gallbladder that results in decreased contractility of the gallbladder and colicky pain in the epigastrium and/or the right upper quadrant of the abdomen (RUQ). FGBD was previously called chronic acalculous cholecystitis, acalculous cholecystitis, or biliary dyskinesia and is a diagnosis of exclusion. Therefore further investigations are routinely performed to exclude other hepatobiliary or gastrointestinal diseases. Experts' consensus developed the Rome Ⅲ criteria in 2006[1] to help guide the management of FGBD. A child who is suspected to have FGBD must experience recurrent episodes of the abdominal pain which last longer than 30 min without relief after bowel movements, postural changes or antacids. The child must have normal liver enzymes, conjugated bilirubin, and amylase/lipase. In addition, the gallbladder must be present and other structural diseases must be excluded. Supportive criteria include the presence of nausea and vomiting, classic biliary pain at RUQ that radiates to the back and/or right infra subscapular region, and pain disturbing sleep[1].

The cholecystokinin-scintigraphy scan (CCK-CS) is generally recommended as a part of the diagnosis for FGBD. The test reports a cut-off value of a gallbladder ejection fraction (GBEF) The cut-off limits that are < 40% suggest the diagnosis of FGBD. FGBD is frequently diagnosed in children with an increase in the number of cholecystectomies performed over the past two decades[2-8]. Several children with a diagnosis of FGBD, however, did not improve their pain symptoms after cholecystectomy[2-8]. The study involves a questionnaire based survey delivered to pediatric gastroenterologist members *via* the PEDGI Bulletin Board, the internet list server. The objective of the study was to explore and to analyze the patterns in decision-making by pediatric gastroenterologists in managing a child with a suspected diagnosis of FGBD.

MATERIALS AND METHODS

This is a questionnaire-based survey distributed to the PEDGI Bulletin Board accessible by hundreds of pediatric gastroenterologists worldwide. The PEDGI Bulletin Board is the internet list server that encourages pediatric gastroenterologists and hepatologists worldwide to communicate with one another electronically. This study was approved by the Institutional Review Board of Johns Hopkins School of Medicine. At the beginning of the questionnaire introduced to the GI bulletin board, only practicing pediatric gastroenterologists (not trainees) were requested and consented themselves to perform the questionnaire. The survey data were collected from the participating PEDGI Bulletin Board users who used the network from January 2011 to April 2011. The survey was completed and analyzed using an Internet-based questionnaire (SurveyMonkey.com, Portland, Oregon, United States). The questionnaire was designed to have participants complete within 10 min.

The survey includes a case history with right upper quadrant pain in Figure 1. The questionnaire consists of 7 questions (Q1-7) in order to observe the patterns of decision-making in managing the case (Figure 1). Q1 gives a direction at the initial step whether the patient should have a test or a medical or surgical treatment performed first. Q2-3 is specifically addressed to the types and the duration of such medical treatments. Q4 is related to the decision-making patterns in investigations. Q5-7 is for their criteria for the CCK-CS and GBEF cut-off limits in diagnosing FGBD and the surgical treatment of FGBD.

RESULTS

The questionnaire survey consisted of 7 questions. One hundred pediatric gastroenterologists participated in the questionnaire study. Of these 100 respondents, 99 completed all questions in the survey, and 71 informed the location of their practices (60 in the United States and 11 from non-United States countries). For Q1 and 2, 19 respondents (19%) decided to treat the abdominal pain with the medical treatment first. Of these 19 respondents, 13 (68.4%) selected proton pump inhibitors (PPI), 8 (42.1%) for antispasmodics, 1 (5.3%) for acetaminophen, 2 for histamine 2 receptor antagonists, 1 for probiotic, 1 for cyproheptadine as their choices of the treatment. In Q3, 17 respondents answered the duration of such a medical treatment. Interestingly, 2 respondents in Q1 referred the patient to a surgeon without further investigations or a treatment trial.

Figure 2 demonstrated the patterns in decision-making of the ordered investigations (Q4). CCK-CS (67.7%) and an upper endoscopy (52.9%) were the most

A 10-year-old girl with recurrent abdominal pain at right upper quadrant for 3 mo is referred to your office by a pediatrician. The pain is described as severe during the episodes, not relieved by bowel movement, postural changes, antacids, typically follows a meal, often lasts 30 min or longer, and radiates to the shoulder and under the tip of the right scapula. Physical exam in general is within normal limits, negative tenderness and negative for Murphy's sign. She has mormal CBC with differential count, comprehensive metabolic panel, and stool guaiac is negative from rectal exam. Abdominal ultrasound is completely negative by all systems.

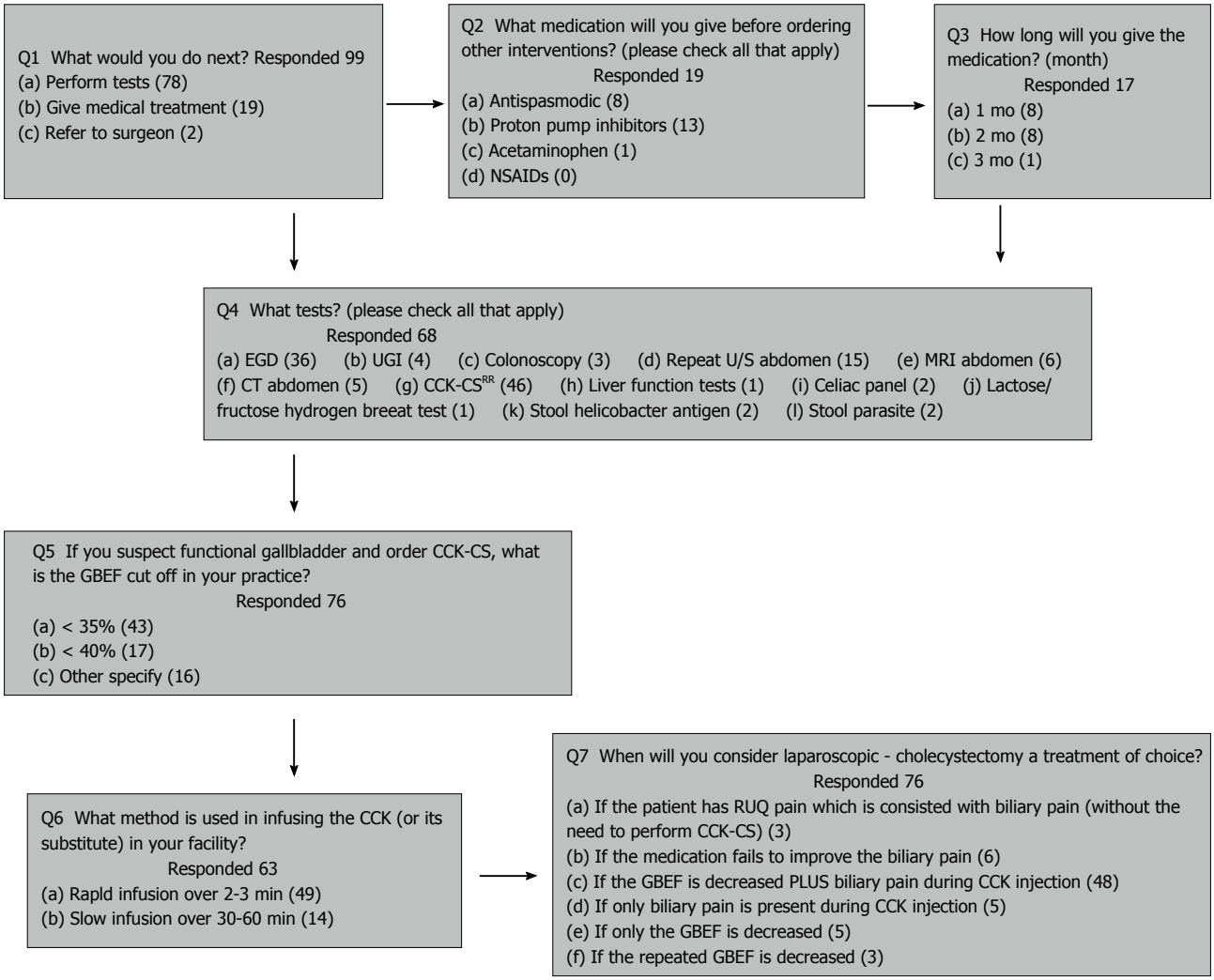


Figure 1 Questionnaire for pediatric gastroenterologists to assess a case with chronic right upper quadrant pain. EGD: Esophagogastroduodenoscopy; UGI: Upper gastrointestinal; U/S: Ultrasonography; MRI: Magnetic resonance imaging; CCK-CS: Cholecystokininscintigraphy scan; GBEF: Gallbladde rejection fraction; RUQ: Right upper quadrant; NSAIDs: Nonsteroidal anti-inflammatory drugs.

commonly ordered tests. Q5-7 indicated the techniques used for CCK-CS and the criteria of GBEF cut-off limits used to diagnose FGBD and to refer to a surgeon for an evaluation for cholecystectomy at their institutions. Seventy-six respondents responded to Q6 and different GBEF cutoff limits were used, < 35% in 43 respondents (56.6%), < 40% in 17 respondents (22.4%), < 30% in 3 respondents, < 25% in 3 respondents, < 20% in one respondent, and < 15% in one respondent (Table 1). Four respondents did not know the GBEF cutoff limits at their institutions. Three respondents decided not to order or to avoid ordering the test, and one respondent did not have the test available at the institution.

Sixty-three respondents responded to Q6. While 49 respondents (77.8%) selected CCK-CS with the rapid infusion of CCK over 2-3 min as the technique used at their institutions, 14 (22.2%) chose the CCK-CS technique with the slow infusion over 30-60 min. For Q7, the majority of respondents (64%) responded by referring the patient to a surgeon with the criteria when both the GBEF value was abnormal and similar types of abdominal pain was reproduced during the infusion of CCK (Figure 3).

DISCUSSION

Several GI diseases and biliary disorders share a similar type of abdominal pain. The presentation of this clinical vignette described in the questionnaire is consistent with FGBD defined by the ROME Ⅲ criteria when all known causes of epigastric and/or RUQ pain are excluded[1]. The patterns in decision-making in managing the case

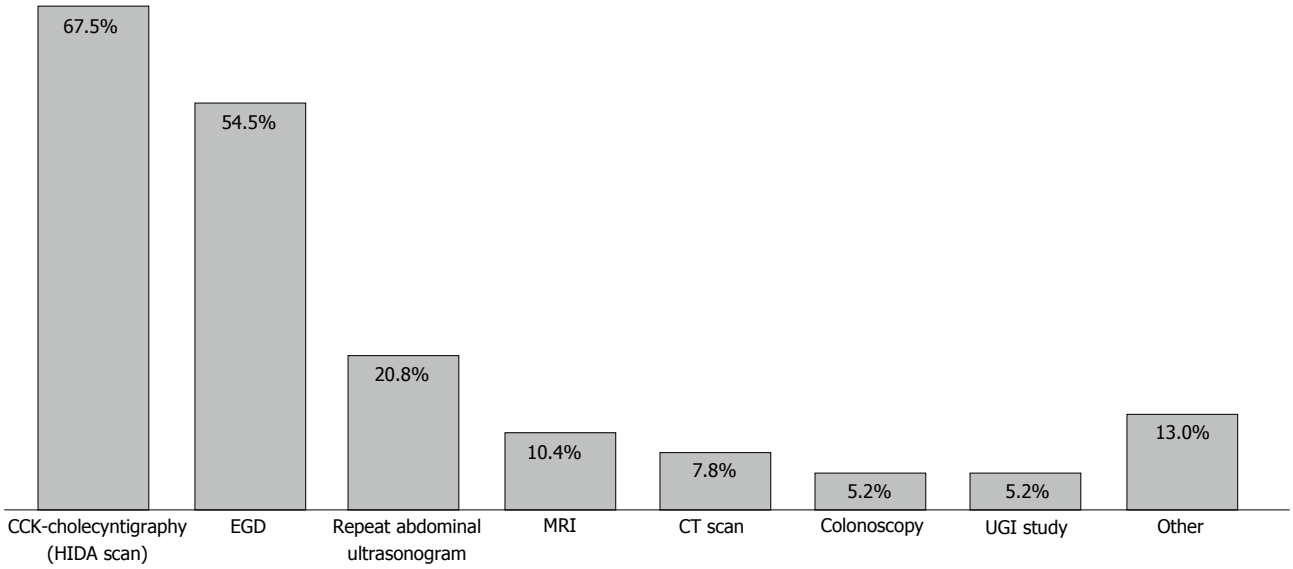


Figure 2 Investigations for chronic right upper quadrant pain in children. CCK: Cholecystokinin; EGD: Esophagogastroduodenoscopy; MRI: Magnetic resonance imaging; CT: Computed tomography; UGI: Upper gastrointestinal; HIDA: Hepatobiliary iminodiacetic acid.

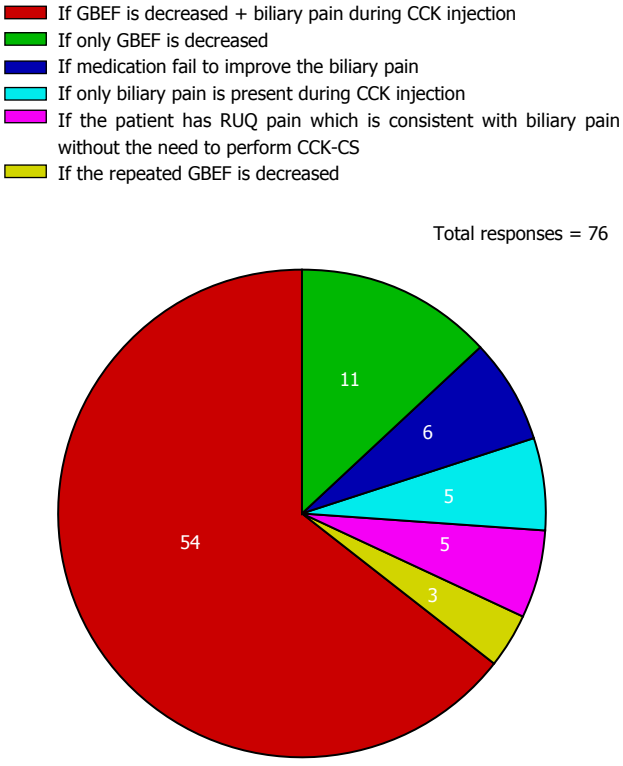


Figure 3 Criteria for referral for a surgical evaluation. GBEF: Gallbladder ejection fraction; CCK: Cholecystokinin; RUQ: Right upper quadrant; CCK-CS: Cholecystokinin scintigraphy scan.

throughout the questionnaire were quite heterogeneous. Interestingly, 2 respondents in Q1 referred the patient to a surgeon without investigations or any treatment trial. Our questionnaire survey demonstrated that only 19% of respondents prescribed PPI or histamine 2 antagonists as the first-line management before performing the tests. This is contrary to other studies which have documented that it is a common practice to empirically treat gastro-

Table 1 Cut-off limits of gallbladder ejection fraction used for criteria to diagnose abnormal gallbladder function

% GBEF used as cut-off	Responses[1]
< 40%	17 (20)
< 35%	47 (55)
< 30%	3 (3.5)
< 25%	4 (4.7)
< 16%	2 (2.4)
< 15%	2 (2.4)

[1]Number of responses for each gallbladder ejection fraction cutoff.

esophageal reflux disease (GERD) and acid peptic disease prior to extensive investigations in such a case when FGBD is suspected[1,9]. Few case reports described children with the diagnosis of FGBD who had a complete relief from the abdominal pain when a PPI was used[10,11].

Further investigations were preferred in the majority of the respondents. It is generally recommended that hepatic function panel (AST, ALT, serum total and direct bilirubin, alkaline phosphatase) amylase/lipase, and an abdominal ultrasound be performed first to exclude hepatobiliary and pancreatic disorders[12,13]. Since these tests were already ordered and reported as normal in the clinical vignette, CCK-CS and an upper endoscopy were observed to be the most common tests chosen by respondents. Biopsies of the proximal GI tract are generally considered even in the absence of gross endoscopic findings as microscopic endoscopic findings may reveal features of eosinophilic gastritis, GERD, *Helicobacter pylori* (*H. pylori*) infection, Crohn's disease, and villus atrophy in those who were also diagnosed with FGBD[10,14,15] to look for mucosal disease that might explain symptoms or improve symptoms when treated. For example, Tutel'ian *et al*[16] reported chronic atrophic gastritis from *H. pylori* infection in patients who were

diagnosed with FGBD prior to the endoscopy. A series of children with FGBD were later diagnosed with Crohn's disease, hiatal hernia, and cyclic vomiting[16], and with esophagitis, *H. pylori* infection and duodenitis after cholecystectomy[17]. Children with functional constipation had a significant impairment of the gallbladder motility[18]. Colonoscopy is usually not required in the absence of lower abdominal pain, chronic diarrhea, or hematochezia[14,15]. As such, an upper endoscopy is recommended to exclude any possible GI diseases which can cause epigastric and/or RUQ pain before a referral to a surgeon for cholecystectomy.

Currently there is no definite guideline in the pediatric practice regarding the appropriate technique performed for the CCK infusion rate and the GBEF cut-off limit in performing a CCK-CS study. The diversity of the techniques used for CCK-CS was observed not only from the questionnaire responses, but experts' consensus such as ROME Ⅲ committee and the Gastrointestinal Council of the Society of Nuclear Medicine. This 3-min rapid CCK infusion and the GBEF cut off limit of < 35% were most common choices in Q5 and Q6, respectively. This rapid infusion technique in theory can cause a severe degree of abdominal pain and nausea in even a healthy subject. This is explained by the fact that CCK slows down the gastric emptying[19,20]. According to the ROME Ⅲ criteria a continuous intravenous CCK infusion over a 30-min period is preferred[1]. On the contrary, the new guidelines from the Gastrointestinal Council of the Society of Nuclear Medicine recommend the slow infusion rate of the CCK over 60 min as the standard test in adults since this technique generates a physiologic response for contraction of the gallbladder and discourage the evidence of the reproducible pain after the CCK injection during CCK-CS[19,21].

Table 1 demonstrates the difference in the GBEF cut-off limits used as the criteria to guide the management for the questionnaire respondents. The GBEF cut-off limits vary from 15%-40% in the reported literature depending on the CCK-CS techniques[22]. When GBEF cut-off limit < 35% was used as an indication for the surgery, the resolution of symptoms was more frequently observed after cholecystectomy in several studies[23]. The cut-off limit of < 15%, however, was a better predictor for a successful outcome after cholecystectomy with negative predictive value of 85%[8]. A CCK provocation test is even a better predictor for the resolution of symptoms than using GBEF cut-off limits alone after cholecystectomy[24]. Reproducible symptoms during the CCK stimulation predicted a symptom relief after cholecystectomy[25,26]. Lyons *et al*[27] reported that 44 children with a stringent GBEF cut-off limit at < 11% had the resolution of symptoms after cholecystectomy. However, there was no observed correlation between with GBEF and the presence of gallbladder pathology such as cholecystitis, cholelithiasis, or cholesterolosis[28]. Interestingly Mahida *et al*[29] reported symptom improvement by 82% of 153 children with FGBD undergoing cholecystectomy regardless of their GBEF values. The number of children undergoing cholecystectomy has increased in the past decade[30]. Despite the safety of laparoscopic cholecystectomy in children, a different risk-benefit ratio should be considered in children with suspected FGBD[31]. Figure 4 demonstrates the algorithm for the best practice management approach in children with suspected FGBD based on our literature review.

There are several limitations in the present study. The sample size was small. Since the survey was voluntary, the respondents were able to withdraw the participation of the questionnaire at any time. Although almost all respondents (99%) responded to Q1, the ambiguity of the question may attribute to the lower response rates in the subsequent questions. FGBD may not be the condition that respondents regularly treat and, therefore, up to one-third of respondents skipped questions without explanations or comments. For Q5-6, the information on the techniques and the cut-off limits of the CCK-CS used at their institutions may not have been available at the time they performed the questionnaire survey.

In our opinion, none of these diagnostic modalities are absolute for the diagnosis of FGBD. Ultimately the decision making for cholecystectomy should be individualized as some patients suffer from severe abdominal pain despite aggressive pain management (Figure 4). As many children who are diagnosed with FGBD may experience recurrent symptoms even after cholecystectomy, they often follow-up with pediatric gastroenterologists or pediatricians and do not have a follow-up with the surgeons who operate them. Therefore, we recommend them to continue to follow-up with both pediatric gastroenterologists and surgeons as a team approach that if no recurrent symptoms are observed within a year after cholecystectomy, the diagnosis of FDGB is confirmed.

The diversity in decision-making among pediatric gastroenterologist respondents in managing the child in this clinical vignette was observed at each step in the questionnaire. A decision for the referral for cholecystectomy should be carefully considered on an individual case basis. The consensus for the guideline in managing children with FGBD may require a team effort among pediatric gastroenterologists, nuclear medicine radiologists, and pediatric surgeons. A multicenter clinical trial study may be necessary to collect longitudinal data in children diagnosed with FGBD. This collaboration will likely shed light on the natural history and the outcome of FGBD in children.

ACKNOWLEDGMENTS

The authors thank all the participants from the PEDGI bulletin board for completing the questionnaires and Robert Whinnery for the manuscript assistance.

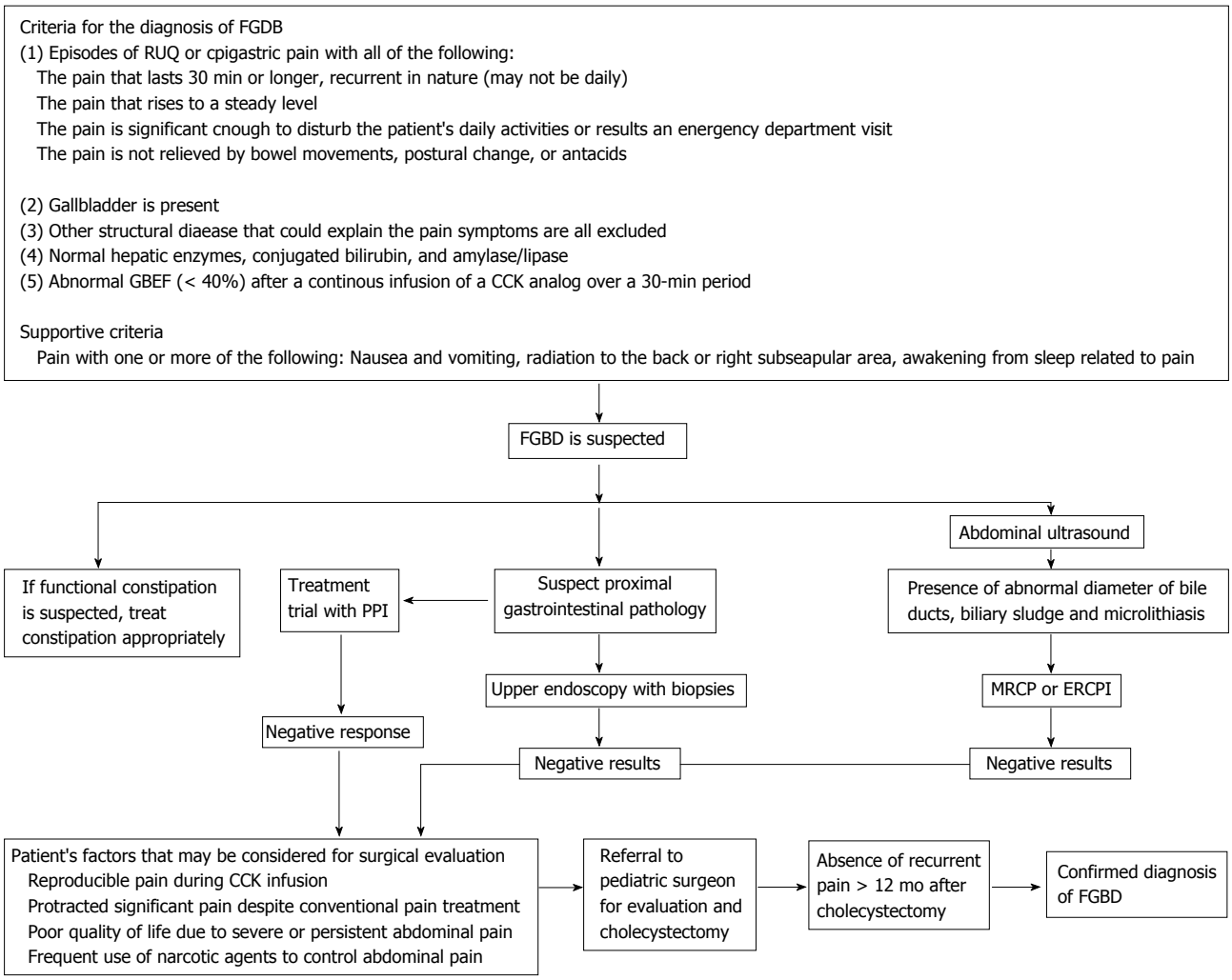


Figure 4 Algorithm for the best practice management approach in children with suspected functional gallbladder disorder (Ref. [1]). FGBD: Functional gallbladder disorder; RUQ: Right upper quadrant; GBEF: Gall bladder ejection fraction; CCK: Cholecystokinin; GERD: Gastroesophageal reflux disease; PPI: Proton pump inhibitor; MRCP: Magnetic resonance cholangipancreatography; ERCP: Endoscopic retrograde cholangipancreatography.

COMMENTS

Background

The rates of cholecystectomy are rising in children with biliary dyskinesia or functional gallbladder disorder (FGBD). FGBD may be a cause of chronic abdominal pain in children and is a diagnosis of exclusion. Not all symptoms of FGBD disappeared after cholecystectomy. The cut-off limits of a gallbladder ejection fraction of the cholecystokinin-scintigraphy scan (CCK-CS) are the key to the diagnosis and the treatment of FGBD. This raises the issue of the accurate interpretation of the test and a thorough investigation to exclude other diseases which have symptoms like FGBD. The study was to explore discrepancy of decision making in managing a case, a scenario of which is consistent with FGBD.

Research frontiers

FGBD is one of the challenging fields in pediatrics. Symptoms overlap with other gastrointestinal disorders such as functional dyspepsia. Limited knowledge in this field of FGBD in children is currently observed in the current medical literature for interpretation of safety and efficacy of the investigations and treatment. There is a need for consensus on symptoms defining and a test diagnosing FGBD. Children with suspected FGBD requires a team approach with primary care physicians, pediatric gastroenterologists and pediatric surgeons. A multicenter randomized controlled trial study comparing medical *vs* surgical management will shed more light to understand the natural history of FGBD. There are several limitations in the present study. The sample size was small. Since the survey was voluntary, the respondents were able to withdraw the participation of the questionnaire at any time. Although almost all respondents (99%) responded to Q1, the ambiguity of the question may attribute to the lower response rates in the subsequent questions. FGBD may not be the condition that respondents regularly treat and, therefore, up to one-third of respondents skipped questions without explanations or comments. For Q5-6, the information on the techniques and the cut-off limits of the CCK-CS used at their institutions may not have been available at the time they performed the questionnaire survey.

Innovations and breakthroughs

This is a pilot study using questionnaire-based survey distributed to the PEDGI Bulletin Board accessible by hundreds of pediatric gastroenterologists worldwide. The PEDGI Bulletin Board is the internet list server that encourages pediatric gastroenterologists and hepatologists worldwide to communicate with one another electronically. FGBD is a rare disease in children. A multicenter randomized controlled trial study comparing medical *vs* surgical management is possible and feasible through the collaborations of a broader network among primary care physicians, pediatric gastroenterologists and pediatric surgeons.

Applications

Based on the result from this study, there was diversity in decision-making among pediatric gastroenterologist respondents in managing the child in this clinical vignette was observed at each step in the questionnaire. A decision for the referral for cholecystectomy should be carefully considered on an individual

case basis.

Terminology

Other terminologies that may be used to describe FGBD include biliary dyskinesia or acalculous cholecystitis.

Peer-review

The authors have nicely summarized the problems clinicians face with the diagnosis and treatment of Functional Gallbladder Disorder. They have also proposed a guideline to help clinicians manage this condition. The publication will aid clinicians in their practice and hence should proceed. It does require minor revisions as it needs to be highlighted that cholecystectomy is ultimately a decision that needs to be made after thorough counseling of the family by the pediatric surgeon.

REFERENCES

1 **Behar J**, Corazziari E, Guelrud M, Hogan W, Sherman S, Toouli J. Functional gallbladder and sphincter of oddi disorders. *Gastroenterology* 2006; **130**: 1498-1509 [PMID: 16678563 DOI: 10.1053/j.gastro.2005.11.063]

2 **Vegunta RK**, Raso M, Pollock J, Misra S, Wallace LJ, Torres A, Pearl RH. Biliary dyskinesia: the most common indication for cholecystectomy in children. *Surgery* 2005; **138**: 726-731; discussion 731-733 [PMID: 16269302 DOI: 10.1016/j.surg.2005.06.052]

3 **Siddiqui S**, Newbrough S, Alterman D, Anderson A, Kennedy A. Efficacy of laparoscopic cholecystectomy in the pediatric population. *J Pediatr Surg* 2008; **43**: 109-113; discussion 113 [PMID: 18206466 DOI: 10.1016/j.jpedsurg.2007.09.031]

4 **Constantinou C,** Sucandy I, Ramenofsky M. Laparoscopic cholecystectomy for biliary dyskinesia in children: report of 100 cases from a single institution. *Am Surg* 2008; **74**: 587-592 [PMID: 18646475]

5 **Cay A**, Imamoglu M, Kosucu P, Odemis E, Sarihan H, Ozdemir O: Gallbladder dyskinesia: a cause of chronic abdominal pain in children. *Eur J Pediatr Surg* 2003; **13**: 302-306 [PMID: 14618519 DOI: 10.1055/s-2003-43576]

6 **Campbell BT**, Narasimhan NP, Golladay ES, Hirschl RB. Biliary dyskinesia: a potentially unrecognized cause of abdominal pain in children. *Pediatr Surg Int* 2004; **20**: 579-581 [PMID: 15322841 DOI: 10.1007/s00383-004-1234-3]

7 **Al-Homaidhi HS**, Sukerek H, Klein M, Tolia V. Biliary dyskinesia in children. *Pediatr Surg Int* 2002; **18**: 357-360 [PMID: 12415355 DOI: 10.1007/s00383-002-0822-3]

8 **Carney DE**, Kokoska ER, Grosfeld JL, Engum SA, Rouse TM, West KM, Ladd A, Rescorla FJ. Predictors of successful outcome after cholecystectomy for biliary dyskinesia. *J Pediatr Surg* 2004; **39**: 813-816; discussion 813-816 [PMID: 15185202 DOI: 10.1016/j.jpedsurg.2004.02.017]

9 **Lake AM**. Chronic abdominal pain in childhood: diagnosis and management. *Am Fam Physician* 1999; **59**: 1823-1830 [PMID: 10208702]

10 **Karnsakul W**, Vaughan R, Kumar T, Gillespie S, Skitarelic K. Evaluation of gastrointestinal pathology and treatment in children with suspected biliary dyskinesia. *Pediatr Surg Int* 2011; **27**: 1307-1312 [PMID: 21706177 DOI: 10.1007/s00383-011-2941-1]

11 **Scott Nelson R**, Kolts R, Park R, Heikenen J. A comparison of cholecystectomy and observation in children with biliary dyskinesia. *J Pediatr Surg* 2006; **41**: 1894-1898 [PMID: 17101366 DOI: 10.1016/j.jpedsurg.2006.06.018]

12 **Vassiliou MC**, Laycock WS. Biliary dyskinesia. *Surg Clin North Am* 2008; **88**: 1253-1272 [PMID: 18992594 DOI: 10.1016/j.suc.2008.07.004]

13 **Sunderland GT**, Carter DC. Clinical application of the cholecystokinin provocation test. *Br J Surg* 1988; **75**: 444-449 [PMID: 3292004 DOI: 10.1002/bjs.1800750516]

14 **Ashorn M**, Mäki M, Ruuska T, Karikoski-Leo R, Hällström M, Kokki M, Miettinen A, Visakorpi JK. Upper gastrointestinal endoscopy in recurrent abdominal pain of childhood. *J Pediatr Gastroenterol Nutr* 1993; **16**: 273-277 [PMID: 8492255 DOI: 10.1097/00005176-199304000-00009]

15 **Squires RH**, Colletti RB. Indications for pediatric gastrointestinal endoscopy: a medical position statement of the North American Society for Pediatric Gastroenterology and Nutrition. *J Pediatr Gastroenterol Nutr* 1996; **23**: 107-110 [PMID: 8856574 DOI: 10.1097/00005176-199608000-00002]

16 **Tutel'ian VA**, Vasil'ev AV, Kochetkov AM, Pogozheva AV, Lysikova SL, Akol'zina SE, Vorob'eva LSh. [Clinical use of flavonoid enriched biologically active food supplements in patients with chronic atrophic gastritis in combination with chronic cholecystitis or bile ducts dyskinesia]. *Vopr Pitan* 2003; **72**: 30-33 [PMID: 12664697]

17 **Singhal V**, Szeto P, Norman H, Walsh N, Cagir B, VanderMeer TJ. Biliary dyskinesia: how effective is cholecystectomy? *J Gastrointest Surg* 2012; **16**: 135-140; discussion 140-141 [PMID: 22042565 DOI: 10.1007/s11605-011-1742-0]

18 **Mehra R**, Sodhi KS, Saxena A, Thapa BR, Khandelwal N. Sonographic evaluation of gallbladder motility in children with chronic functional constipation. *Gut Liver* 2015; **9**: 388-394 [PMID: 25167798 DOI: 10.5009/gnl13414]

19 **Ziessman HA**, Muenz LR, Agarwal AK, ZaZa AA. Normal values for sincalide cholescintigraphy: comparison of two methods. *Radiology* 2001; **221**: 404-410 [PMID: 11687683 DOI: 10.1148/radiol.2212010154]

20 **Richmond BK**. Optimum utilization of cholecystokinin cholescintigraphy (CCK-HIDA) in clinical practice: an evidence based review. *W V Med J* 2012; **108**: 8-11 [PMID: 22655428]

21 **DiBaise JK**, Richmond BK, Ziessman HA, Everson GT, Fanelli RD, Maurer AH, Ouyang A, Shamamian P, Simons RJ, Wall LA, Weida TJ, Tulchinsky M. Cholecystokinin-cholescintigraphy in adults: consensus recommendations of an interdisciplinary panel. *Clin Nucl Med* 2012; **37**: 63-70 [PMID: 22157031 DOI: 10.1097/RLU.0b013e31823e26bb]

22 **Telega G**. Biliary dyskinesia in pediatrics. *Curr Gastroenterol Rep* 2006; **8**: 172-176 [PMID: 16533482 DOI: 10.1007/s11894-006-0015-7]

23 **Haricharan RN**, Proklova LV, Aprahamian CJ, Morgan TL, Harmon CM, Barnhart DC, Saeed SA. Laparoscopic cholecystectomy for biliary dyskinesia in children provides durable symptom relief. *J Pediatr Surg* 2008; **43**: 1060-1064 [PMID: 18558183 DOI: 10.1016/j.jpedsurg.2008.02.032]

24 **Morris-Stiff G**, Falk G, Kraynak L, Rosenblatt S. The cholecystokin provocation HIDA test: recreation of symptoms is superior to ejection fraction in predicting medium-term outcomes. *J Gastrointest Surg* 2011; **15**: 345-349 [PMID: 20824367 DOI: 10.1007/s11605-010-1342-4]

25 **Gurusamy KS**, Junnarkar S, Farouk M, Davidson BR. Cholecystectomy for suspected gallbladder dyskinesia. *Cochrane Database Syst Rev* 2009; (**1**): CD007086 [PMID: 19160318 DOI: 10.1002/14651858.CD007086.pub2]

26 **Krishnamurthy GT**, Krishnamurthy S: Extended application of 99mTc-mebrofenin cholescintigraphy with cholecystokinin in the evaluation of abdominal pain of hepatobiliary and gastrointestinal origin. *Nucl Med Commun* 2010; **31**: 346-354 [DOI: 10.1097/MNM.0b013e32832fa2c0]

27 **Lyons H**, Hagglund KH, Smadi Y. Outcomes after laparoscopic cholecystectomy in children with biliary dyskinesia. *Surg Laparosc Endosc Percutan Tech* 2011; **21**: 175-178 [PMID: 21654301 DOI: 10.1097/SLE.0b013e31821db7b2]

28 **Jones PM**, Rosenman MB, Pfefferkorn MD, Rescorla FJ, Bennett WE. Gallbladder Ejection Fraction Is Unrelated to Gallbladder Pathology in Children and Adolescents. *J Pediatr Gastroenterol Nutr* 2016; **63**: 71-75 [PMID: 26670710 DOI: 10.1097/MPG.0000000000001065]

29 **Mahida JB**, Sulkowski JP, Cooper JN, King AP, Deans KJ, King DR, Minneci PC. Prediction of symptom improvement in children with biliary dyskinesia. *J Surg Res* 2015; **198**: 393-399 [PMID: 25891671 DOI: 10.1016/j.jss.2015.03.056]

30 **Walker SK**, Maki AC, Cannon RM, Foley DS, Wilson KM, Galganski LA, Wiesenauer CA, Bond SJ. Etiology and incidence of pediatric gallbladder disease. *Surgery* 2013; **154**: 927-931; discussion 931-933 [PMID: 24074432 DOI: 10.1016/j.surg.2013.04.040]

31 **Srinath A**, Saps M, Bielefeldt K. Biliary dyskinesia in pediatrics. *Pediatr Ann* 2014; **43**: e83-e88 [PMID: 24716563 DOI: 10.3928/00904481-20140325-09]

P- Reviewer: Singhal V, Wang R **S- Editor**: Qi Y **L- Editor**: A
E- Editor: Li D

Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com