Article

Opportunities for Comprehensive Medication Management (CMM) for Children with Special Healthcare Needs and Medical Complexity (CSHCN-CMC): The Methodology of a Prospective Case Series within a Collaborative Practice Agreement (CPA)

Jena Quinn [1]*, Heather Monk Bodenstab [1,2], Catherine Kuhn [3], and Richard H. Parrish II [4]*

[1] Perfecting Pediatrics, LLC, Haddon Heights, NJ, 08035, USA; jquinn@perfectingpeds.com;
[2] Department of Medical Sciences, Sobi Pharma, Inc., Waltham, MA 02451, USA; heather.bodenstab@sobi.com;
[3] Custom Health, Inc., Mountain View, CA 94043, USA; cathy.kuhn@customhealth.com;
[4] Department of Biomedical Sciences, Mercer University School of Medicine, Columbus, GA 31902, USA
* Correspondence: parrish_rh@mercer.edu; Tel. +1 (706) 223-5185; jquinn@perfectingpeds.com; Tel. +1 (856) 217-7533

Abstract: Care coordination (CC) for children with special healthcare needs and medical complexity (CSHCN-CMC) is challenging, and medication management is especially difficult for providers, parents/caregivers, and patients alike. While numerous strategies for CC have been suggested and implemented, barriers to medication optimization remain. The report describes the creation of a pediatric clinical pharmacotherapy practice, related standard operating procedures to assure consistent application of screening tools and care provision through comprehensive medication management (CMM), and establishment of a collaborative practice agreement (CPA) to guide drug therapy delegation, monitoring, and modification. The methodology of a prospective case series is also presented to highlight drug therapy problems and their resolution in CSHCN-CMC. Future opportunities to expand the practice for engagement in population health management as well as prior authorization activities on behalf of physicians will be discussed.

Keywords: CSHCN; CMC; care coordination; case series; collaboration; medical complexity; medication management; methodology; pediatrics

1. Introduction and Statement of the Problem

Care coordination (CC) for children with special healthcare needs and medical complexity (CSHCN-CMC) has been especially challenging in recent years, and many unmet needs continue to exist in this general population as well as sub-populations affected by multimorbidity and polypharmacy [1-8]. These patients account for almost 30% of all pediatric healthcare costs while representing about 1% of the pediatric population [9,10]. Numerous strategies have been employed recently to improve care access and reduce adverse events, including patient-centered medical homes (PCMH) [11-13], telemedicine [14], and multidisciplinary team-based care [15], among others. CSHCN-CMC often are administered multiple medications, many of which are liquid compounded nonsterile preparations (pCNSPs) [16,17]. Assuring continuity of care at care transitions for safe medication management has been identified as an often-daunting task for parents, caregivers, and the patient's healthcare team [18–27]. Suggestions for implementing, sustaining, and improving medication management have been forwarded in order to encourage development of a child-friendly medication use system, including

 doi:10.20944/preprints202211.0196.v1

- creation of interprofessional communities of practice and research that share tacit medication management knowledge through various synchronous and asynchronous delivery media to promote point-of-care collaboration and coordination;

- application of administrative leadership and vision that promotes an environment of innovation through sustainable provider-patient-payer partnerships and outcomes-driven system transformation; and

- adoption and expansion of patient engagement functionalities that align with the 21st Century Cures Act and the World Health Organization's Convention on the Rights of the Child for increasing choice, access, equity, and quality in health care [28].

The purpose of this report is to describe the methodology of a pediatric pharmacotherapy practice focused on provision of comprehensive medication management (CMM) through establishment of a collaborative practice agreement (CPA) for patients admitted to a long-term care facility with CSHCN-CMC [29].

1.1 Focus on reduction in hospital readmissions

After the 2012 implementation of the Hospital Readmissions Reduction Program by the Centers for Medicare and Medicaid services, many organizations implemented strategies and programs to reduce readmission rates but were mostly directed at Medicare beneficiaries and for specific conditions [30–35]. Of the pediatric initiatives launched, most were limited to inpatient readmissions from home and likely did not account for readmissions in patients who were discharged from a rehabilitation/transitional care hospital or medical home [36]. Additionally, initiatives typically evaluate the readmission rate at the same hospital a patient was discharged from. Children with CMC may often go to different hospitals for admission, depending on the type and severity of issue. Different hospital readmissions differentially affect hospitals' pediatric readmission rates and may prevent appropriate quality assessment and improvement [37].

From 2010 to 2016, the total number of pediatric admissions in the United States Healthcare Cost and Utilization Project Nationwide Readmissions Database decreased by 21.3%, but the percentage of admissions for children with complex chronic conditions increased by 5.7% [38]. The 30-day readmission rate, overall, increased and was associated with greater numbers of admissions for children with chronic conditions. This is not surprising given that children with chronic disease are living longer and developing long-term consequences of their diagnoses and are more likely than other children to be readmitted after an acute care hospitalization [38–40].

Thirty-day hospital readmission rates in children with complex chronic conditions vary from 13% to 40% based on the degree of medical complexity and technology dependence [41–43]. Hospital readmission accounts for the largest share of subsequent costs after an index hospitalization, payers are targeting this metric to reduce unnecessary health care spending [10,41,42].

1.2 Impact on adverse event reduction

Adverse drug reactions are known to be a cause of hospital admission in pediatric patients and various incidences of ADR-related hospitalizations have been reported [44–47]. Most studies include large numbers of patients receiving chemotherapy, except for the study completed by Gholami and colleagues with less than 8% of children exposed to chemotherapeutic agents [48]. In this study, authors prospectively evaluated pediatric

 doi:10.20944/preprints202211.0196.v1

hospital readmissions secondary to adverse drug events and determined more than a third of the adverse drug events were preventable. Zandieh and colleagues evaluated potential risk factors for children experiencing an adverse drug event in the ambulatory setting. They found 14% experienced an ADE, of which 23% were preventable. Children with multiple prescriptions were at an increased risk of having a preventable ADE, controlling for parental education, racial/ethnic, English proficiency, practice type and duration of care [49].

1.3 Impacts of off-label and unlicensed medication use in children

The incidence of adverse drug reactions may also be affected by the high rate of off-label and unlicensed medication use in the pediatric population. A recent literature review aimed to estimate the rates of pediatric off-label and unlicensed drug use [50]. Many studies reported high rates of off-label (up to 78.7%) and unlicensed (up to 35%) drug use in different pediatric patient settings [51]. The lack of clinical safety and efficacy data for the indication and age range, as well as the dose, dosage form and route of administration, places these children at increased risk for adverse events. Children with CMC receive more daily medications, which would intuitively place them at even higher risk of ADEs.

1.4 Impacts of complex care plans

Children with CMC often have intricate, complex care plans including multiple medications, various subspecialty involvement and technology dependence which can make discharge to home difficult. These children may be transitioned from acute care hospitals to subacute transitional hospitals or medical homes but readmission rate to the referring acute care hospital has been infrequently documented in the literature. Jurgens and colleagues evaluated the acute care hospital readmission rate in children with complex chronic conditions discharged to home from subacute care facilities [41]. Nearly one-fifth of children with at least one complex chronic condition had 1 or more readmissions within 30 days of discharge. Authors specifically identified the number of discharge medications as a significant risk factor as the hospital readmission rate was 29% in children discharged home on 8 or more medications. This is an area where pediatric pharmacists trained in the care of children with complex chronic conditions can have a major impact, by eliminating unnecessary medications, reducing polypharmacy, medication reconciliation, discharge medication counseling for families and prevention of adverse drug events.

Stone and colleagues evaluated admission medication reconciliation in children with medically complex conditions [52]. These children are known to have frequent hospitalizations, to be on multiple medications and at higher risk for errors and ADEs [49,53–56]. Children with CMC averaged 5.3 chronic medications with an average reconciliation process time of 90 minutes, much longer than the amount of time typically dedicated to this process in clinical practice. About 21% of admission orders were incorrect and affected more than half of the patients studied. Life threatening or potentially serious ADEs could have occurred in 22% of patients but were luckily prevented due to the prospective nature of the study. This study shows the importance of prescriber and pharmacist interaction during the medication reconciliation process in these complex children, and that more in-depth reviews of medication lists results in error prevention.

2. Methods and materials

2.1 Targeted long-term care facility description

Long-term facilities (LTC) provides skilled nursing along with rehabilitative care and a respiratory care program. LTC addresses issues such as growth, development,

 doi:10.20944/preprints202211.0196.v1

educational, pulmonary management which can be complicated by the child's medical fragility. Children at LTC often have:

- Degenerative diseases
- Critical airway (tracheotomy)
- Mechanical ventilator dependency
- Traumatic brain injury
- Complex seizure disorders
- Neuromuscular diseases
- Chromosomal disorders
- Near drowning
- BPD (Bronchopulmonary Dysplasia)
- Orthopedic anomalies and conditions
- Neurological impairments
- Craniofacial anomalies
- Terminal illnesses
- Wound care needs
- IV therapy including Total Parenteral Nutrition (TPN)

2.2 Protocol description

A prospective case series methodology will be employed to study clinical pharmacist interventions and care process for CSHCN-CMC [57]. The review protocol described below will be used to (1) illustrate the methods in which patients are identified for review, (2) document key performance areas unique to the CSHCN-CMC population, (3) tabulate the common types of drug therapy problems encountered and managed, and (4) summarize the clinical outcomes associated with the medication review and intervention. One hundred consecutive cases meeting the following inclusion and exclusion criteria will be enrolled at one pediatric long-term care facility:

Inclusion criteria:

At least two chronic medical conditions;
At least five scheduled medications;
At least four drug therapy problems (DTPs) [58];
Unnecessary drug therapy;
Needs additional drug therapy;
Ineffective drug therapy;
Dosage too low;
Adverse drug effect;
Dosage too high or duration too long;
Lack of adherence.

Exclusion criteria:

Patient or guardian refused to participate.

Copies of actual chart documentation of the pharmacist's workup of drug therapy will be reviewed and tabulated (JQ and HMB) using a DTP scoring sheet. Descriptive statistics will be used for patient demographics and DTP frequency distributions. A copy of the informed consent form for CMM through CPA is found in Supplementary file A.1.

2.1 Standard operating procedure for comprehensive medication management (CMM) within a collaborative practice agreement (CPA) in a CSHCN-CMC patient - Perfecting Peds, L.L.C.

 doi:10.20944/preprints202211.0196.v1

The purpose of this SOP is to provide a standard process for the pharmacist's work-up of a CSHCN-CMC patient's drug therapy. The primary aim is to identify the patient's drug-related needs, determine potential or actual drug therapy problems, create a plan for the optimization of drug therapy, including establishing therapeutic goals, and provide a template for documentation in the patient's healthcare record.

Many children with life-limiting conditions are now living longer because of advances in healthcare and technological innovations. These children are characterized by multimorbidity, higher health care use, and technological dependency. Their complexity and fragility lead to higher risks for medication errors. High rates of fragmented care provision, miscommunication, and polypharmacy in CMC increase opportunities for error, particularly as children transition between health care settings and practitioners. These children typically have at least two chronic conditions and receive at least five scheduled medications daily.

2.2 Patient care process for pharmacist's work-up of drug therapy. (Lexi-Comp Pediatrics will be used as the primary source of drug information.)

A. Identify a patient needing review in the following ways:
   - A.1. At transition of care (via email notification);
   - A.2. Initial review of new patient;
   - A.3. Monthly follow-up review;
   - A.4. Provider or nurse-generated request for a focused review

B. Review the prior note of pharmacists

C. Review the prior notes of physicians

D. Review labs and consultant notes. Use access to surrounding healthcare systems to review recent admissions and doctor appointments

E. Review dietician's note for dietary considerations (food allergies and intolerances, fluid requirements, and macronutrient, caloric and protein needs) and supplemental electrolytes, trace elements, and vitamins using the flowing reference as a guide:
   - E.1. Dietary Reference Intakes (DRIs): Recommended Dietary Allowances and Adequate Intakes, Elements. Food and Nutrition Board, National Academies (https://www.ncbi.nlm.nih.gov/books/NBK545442/table/appJ_tab3/?report=objectonly)
   - E.2. Nutrient Recommendations: Dietary Reference Intakes (DRI) (https://ods.od.nih.gov/HealthInformation/nutrientrecommendations.aspx#dri)
   - E.3. Focus on calcium, phosphorus and vitamin D intake given the risk of immobility-induced osteopenia/osteoporosis in these complex patients
   - E.4. Growth charting: CDC recommends that health care providers:
     - E.4.1. Use the WHO growth standards to monitor growth for infants and children ages 0 to 2 years of age in the U.S. (https://www.cdc.gov/growthcharts/who_charts.htm#print)
     - E.4.2 Use the CDC growth charts for children age 2 years and older in the U.S. (https://www.cdc.gov/growthcharts/clinical_charts.htm#Set1)
   - E.5. Use the dieticians note and labs to determine if electrolyte, vitamin and mineral supplementation is appropriate
   - E.6 Review timing of electrolyte, vitamin and mineral administration in the medication administration record to ensure binding reactions do not occur and prevent intestinal absorption (e.g. separating calcium and phosphorus supplements by at least 2 hours, etc.).

F. Review EHR dashboard for vital signs and trends

 doi:10.20944/preprints202211.0196.v1

G. Review each medication order, line by line. Ensure each medication has the appropriate:
  G.1. Indication or necessity - Match medical conditions with drug therapies or continued need for a medication
    G.1.1. If a medication has no associated reason for use, initiate deprescribing process (https://deprescribing.org/resources/deprescribing-guidelines-algorithms/)
  G.2. Drug
  G.3. Concentration (in micrograms or milligrams per mL)
  G.4. Dose
    G.4.1. Perform dose range checking: Ensure patient has not outgrown dose. If the patient's weight has increased by more than 10% since the medication was prescribed, weight adjust if clinically indicated. If the patient's weight has increased by more than 20% since the medication was prescribed and below the typical dosing range, the dose may be subtherapeutic and necessity of the medication should be assessed.
  G.5. Dosage form
    G.5.1.Patients on a ketogenic diet need a lower carbohydrate, sugar free formulation
    G.5.2.Safer alternatives may exist if the patient receives numerous suspensions (such as capsules or tablets). If possible, avoid suspensions with multiple compounded concentrations.
  G.6. Route
    G.6.1. Many medications have reduced absorption or are not absorbed in the jejunum or duodenum. Refer to absorption chart for specific literature per medication [59,60]. Identify patients that have been stabilized on medications being given via an enteric route which may not have optimal or may have limited published literature. For those medications, a discussion must occur with the team regarding the route of administration. There may be times where moving medication administration from the jejunum to gastric or duodenal routes may significantly increase the bioavailability of the medication which may cause adverse effects.
    G.6.2. If administered via a tube, consider special instructions needed for RN to administer correctly.
    G.6.3 Certain medication formulations may significantly bind to enteral feed tubing. Review drug dosing reference or prescribing information from manufacturer as this may alter the dosing formulation that should be prescribed or may require additional water flushing of the tube (e.g. ciprofloxacin suspension binds extensively to tubing and patients that require enteral feeding tube administration should be transitioned to the tablet formulation, Epidiolex® requires avoided tubes made of PCV or silicone NG tubes < 50 cm in length or 5 < FR in diameter with 5 times the priming volume of room temperature water after each dose, etc).
  G.7. Frequency - simplify for RN if possible.
G.8. PRN use to evaluate need for change in regimen (ex. Increase seizure rescue medications or bowel regimen change if increase in suppository/ enema use).
  G.8.1. Check PRN report for unused medications and potential PRN discontinuation
G.9. Drug-drug interaction check for all medications: these patients are prescribed numerous medications with anticholinergic or serotonergic properties (https://www.drugs.com/drug_interactions.html)

 doi:10.20944/preprints202211.0196.v1

G.9.1. Common anticholinergic agents: glycopyrrolate, ipratropium, diphenhydramine, cetirizine, loratadine
G.9.2. Antipsychotics and promotility agents for serotonin syndrome [61]
G.9.2.1. Common symptom clusters include:
G.9.2.1.1. Altered mental status
G.9.2.1.2. Neuromuscular abnormalities
G.9.2.1.3. Autonomic hyperactivity

H. Review timing of medications/supplements in EHR
H.1 Ensure avoidance of drug binding
H.1.1 Sucralfate and any other medications
H.1.2 Calcium, phosphorus, magnesium, iron
H.1.3 Levothyroxine
H.2 Decrease number of individual medication administrations per day (where applicable based on nursing staff and patient tolerance)
H.3 Consider frequency of feeds (intermittent bolus versus continuous) and timing of medications
H.3.1 Dosing references may suggest that feeds be held for certain medications to avoid a significant decrease in bioavailability of the medication. The appropriateness of holding feeds must be assessed based on medication titration and patient tolerance (e.g. dosing references suggest holding feeds for levothyroxine administration—this may or may not be appropriate based on how the drug has been titrated or if the patient can tolerate holding feeds based on serum glucoses, etc.)

I. Monitor for common adverse drug reactions (ADRs): Risk for ADRs in children with medical complexity include [62,63]:
I.1. History of a previous adverse drug reaction
I.2. Younger age
I.3. Impairment of liver or renal function
I.4. Polypharmacy
I.5. Female sex
I.6. Certain genetic polymorphisms (2D6, 2C9, 2C19)
I.7. General anesthetic use
I.8. Off-label drug use
I.9. Assess for predictability or preventability
I.91. Predictable ADR
I.9.1.1. Side effect
I.9.1.2. Secondary effect
I.9.1.3. Interaction
I.9.1.4. Toxicity
I.9.2. Unpredictable
I.9.2.1. Intolerance
I.9.2.2. Allergic/pseudo allergic
I.9.2.3. Idiosyncratic
I.9.2.4. Psychogenic
I.10. If a laboratory value is outside the normal range, assess for medication induced and develop a plan to titrate or alternate medication with providers

J. Write pharmacist medication management note:
J.1. Three level notes
J.1.1. Changes covered under the CPA – modify, discontinue create orders per CPA
J.1.2. Changes recommended pending MD approval outside of CPA

 doi:10.20944/preprints202211.0196.v1

J.1.3. Changes recommended with sub specialist approval. Note time and date subspecialist was contacted

J.2. Therapeutic goal setting;

J.2.1. For each drug therapy problem identified, establish a written goal using the following scale:

J.2.1.1. Reduce or eliminate signs or symptoms

J.2.1.2. Slow or halt the progression of a disease;

J.2.1.3. Prevent a disease;

J.2.1.4. Normalize laboratory values;

J.2.1.5. Assist with the diagnostic process.

3. Discussion

Numerous opportunities exist for collaborative comprehensive medication management (CMM) for CSHCN-CMC. Benavides and others described a methodology for the establishment of pediatric medication therapy management services due to the rising prevalence of chronic diseases in children, including various thresholds for patient eligibility based on a chronic disease profile and medication burden [65]. Lampkin and team identified opportunities and barriers to practice implementation in an office setting, including pearls for site selection, business planning, pharmacist practice functions through CPAs, and regulatory/legal aspects [66]. Aboneh and Chui first studied the problem of unmet prescription medication needs systematically, finding that patients with unmet CC need were almost four times more likely to have an unmet need for prescription medications [22]. In an observational study, Solano and colleagues described the impact of pharmacist medication review and identified inappropriate drug administration (32.3%), herb-drug interactions (24.6%) and dose selection (17%) as the most frequent drug therapy problems. Further, parents' knowledge about medications rose by 28% after pharmacist's medication counselling and administration and side effects decreased by 67% and 49%, respectively [26].

Feinstein and colleagues used a Medication Regimen Complexity Index (MRCI), comprised of 3 sub-scores for dosage form, dose frequency, and specialized instructions, to identify potentially modifiable factors associated with suboptimal therapies. They found a median (IQR) of 6 (4-7) dosage forms per patient, 7 (5-9) dose frequencies per patient, and 5 (4-8) instructions per patient, with significantly higher counts among higher MRCI groups [23]. Feinstein and Orth discussed provider- and system-level recommendations to improve medication safety in CSHCN-CMC [67]. At the point of care, they suggest generation of the best possible medication list, increasing the ease of medication administration, and defining targets to measure treatment success. At the systems-level, integrated pharmacist support to provide CMM, technology and telehealth-based education and observation, and improved adverse event surveillance. In a retrospective, randomized, proof-of-concept study conducted within a large pediatric primary care clinic, Marquez and associates identified common drug therapy problems in 100 patients, including drug use without an indication, nonoptimized or duplicate therapy, undertreated symptoms, adverse drug events, and clinically significant drug-drug interactions. Pharmacist provision of medication management significantly reduced regimen complexity, especially for those with high medication burden [27]. Each of these studies provides a blueprint for the creation of durable CPAs through a standardized process for care provision and documentation afforded by CMM.

The inclusion of organization-wide processes to improve medication management throughput exist with the implementation of appropriate therapeutic interchanges, where one medication is identified as the agent of first choice within a therapeutic class. In addition, pharmacist completion of prior authorization requests on behalf of the physician can

 doi:10.20944/preprints202211.0196.v1

address and/or remove adherence barriers often present within the CSHCN-CMC population due to the need for non-formulary medications which may be off-label, but necessary for appropriate care provision [68].

Opportunities to improve the quality of health care delivered and thereby, promote better health outcomes for long-term care CSHCN-CMC patients may lie in the practice's leadership in implementing data-driven processes for population health management [69]. These processes will include:

- Development of quality improvement initiatives to promote systematic change across the practice and organization;
- Implementation of academic detailing on focused drug topics;
- Creation of clinical decision support to promote best practices; and
- Identification of targeted clinical interventions, for example, vaccination promotion and optimization.

4. Conclusion and next steps

We present the methodology of a prospective case series in which a standardized process for comprehensive medication management (CMM) will be utilized in CSHCN-CMC patients through a collaborative practice agreement (CPA). In this observational study, each patient or legal guardian will be consented for participation, and the protocol and study methodology will be reviewed by the Institutional review Board of Mercer University. A case series of 107 CSHCN-CMC patients was chosen in order to describe the practice of a clinical pharmacist for identifying, preventing, and/or resolving drug therapy problems in these highly complex patients. The study will be registered at Research Registry (www.researchregistry.com) and will be conducted in accordance with the Declaration of Helsinki. Further, testable hypotheses related to drug therapy management processes and techniques will be identified for future randomized studies, and population health strategies for system-wide implementation of optimal collaborative medication management will be trialed.

Author Contributions: All authors contributed to the conceptualization, writing, and editing of this manuscript. All authors have read and agreed to the published version of the manuscript. The final manuscript was approved by Perfecting Peds, LLC.

Funding: This work received no external funding.

Institutional Review Board Statement: Mercer University IRB will review the protocol for the prospective case series study.

Informed Consent Statement: Informed consent will be obtained from each patient whose drug therapy is reviewed and managed.

Data Availability Statement: Deidentified data will be available upon request.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Kuo, D. Z.; McAllister, J. W.; Rossignol, L.; Turchi, R. M.; Stille, C. J. Care Coordination for Children With Medical Complexity: Whose Care Is It, Anyway? *Pediatrics*. **2018**, *141* (Supplement_3), S224–S232. https://doi.org/10.1542/peds.2017-1284G.
2. Miller, R.; Tumin, D.; Hayes, D.; Uffman, J. C.; Raman, V. T.; Tobias, J. D. Unmet Need for Care Coordination Among Children with Special Health Care Needs. *Popul. Health Manag*. **2019**, *22*, 255–261. https://doi.org/10.1089/pop.2018.0094.
3. Pankewicz, A.; Davis, R. K.; Kim, J.; Antonelli, R.; Rosenberg, H.; Berhane, Z.; Turchi, R. M. Children With Special Needs: Social Determinants of Health and Care Coordination. *Clin. Pediatr. (Phila).* **2020**, *59*, 1161–1168. https://doi.org/10.1177/0009922820941206.

4. Stewart, K. A.; Bradley, K. W. v; Zickafoose, J. S.; Hildrich, R.; Ireys, H. T.; Brown, R. S. Care Coordination for Children with Special Needs in Medicaid: Lessons from Medicare. *Am. J. Manag. Care.* **2018,** *24*, 197–202.
5. Turchi, R. M.; Berhane, Z.; Bethell, C.; Pomponio, A.; Antonelli, R.; Minkovitz, C. S. Care Coordination for CSHCN: Associations With Family-Provider Relations and Family/Child Outcomes. *Pediatrics*. **2009**, *124* (Supplement_4), S428–S434. https://doi.org/10.1542/peds.2009-1255O.
6. Moeenuddin, Z.; Kim-Kupfer, C.; Owchar, E.; Baker, J.; Duffield, A.; Santoro, T. The Influence of Care Coordination on Patients With Special Health Care Needs in a Pediatric Residency Continuity Clinic. *Glob. Pediatr. Health*. **2019**, *6*, 2333794X1984867. https://doi.org/10.1177/2333794X19848677.
7. Hofacer, R. D.; Panatopoulos, A.; Vineyard, J.; Tivis, R.; Nguyen, E.; Jingjing, N.; Lindsay, R. P. Clinical Care Coordination in Medically Complex Pediatric Cases: Results From the National Survey of Children With Special Health Care Needs. *Glob. Pediatr. Health*. **2019**, *6*, 2333794X1984791. https://doi.org/10.1177/2333794X19847911.
8. Davies, S. C.; Lundine, J. P.; Justice, A. F. Care Coordination for Children with Special Health Care Needs: A Scoping Review to Inform Strategies for Students with Traumatic Brain Injuries. *J. School Health*. **2022**, *92*, 270–281. https://doi.org/10.1111/josh.13132.
9. Berry, J. G.; Hall, M.; Neff, J.; Goodman, D.; Cohen, E.; Agrawal, R.; Kuo, D.; Feudtner, C. Children With Medical Complexity And Medicaid: Spending And Cost Savings. *Health Aff.* **2014**, *33*, 2199–2206. https://doi.org/10.1377/hlthaff.2014.0828.
10. Cohen, E.; Berry, J. G.; Camacho, X.; Anderson, G.; Wodchis, W.; Guttmann, A. Patterns and Costs of Health Care Use of Children With Medical Complexity. *Pediatrics*. **2012,** *130*, e1463–e1470. https://doi.org/10.1542/peds.2012-0175.
11. Ross, S. M.; Smit, E.; Twardzik, E.; Logan, S. W.; McManus, B. M. Patient-Centered Medical Home and Receipt of Part C Early Intervention Among Young CSHCN and Developmental Disabilities Versus Delays: NS-CSHCN 2009–2010. *Matern. Child Health J.* **2018,** *22*, 1451–1461. https://doi.org/10.1007/s10995-018-2540-z.
12. Leyenaar, J. A. K.; O'Brien, E. R.; Leslie, L. K.; Lindenauer, P. K.; Mangione-Smith, R. M. Families' Priorities Regarding Hospital-to-Home Transitions for Children with Medical Complexity. *Pediatrics.* **2017**, *139*. https://doi.org/10.1542/peds.2016-1581.
13. Guerrero, A. D.; Zhou, X.; Chung, P. J. How Well Is the Medical Home Working for Latino and Black Children? *Matern. Child Health J.* **2018**, *22*, 175–183. https://doi.org/10.1007/s10995-017-2389-6.
14. Mosquera, R. A.; Avritscher, E. B. C.; Pedroza, C.; Lee, K. H.; Ramanathan, S.; Harris, T. S.; Eapen, J. C.; Yadav, A.; Caldas-Vasquez, M.; Poe, M.; Martinez Castillo, D. J.; Harting, M. T.; Ottosen, M. J.; Gonzalez, T.; Tyson, J. E. Telemedicine for Children With Medical Complexity: A Randomized Clinical Trial. *Pediatrics*. **2021**, *148*. https://doi.org/10.1542/peds.2021-050400.
15. Hobart, C. B.; Daines, C. L.; Phan, H. Developing Future Clinical Pharmacy Leaders in the Interprofessional Care of Children with Special Health Care Needs and Medical Complexity (CSHCN-CMC) in a Pediatric Pulmonary Center. *Children.* **2019**, *6*, 135. https://doi.org/10.3390/children6120135.
16. Feinstein, J. A.; Hall, M.; Antoon, J. W.; Thomson, J.; Flores, J. C.; Goodman, D. M.; Cohen, E.; Azuine, R.; Agrawal, R.; Houtrow, A. J.; DeCourcey, D. D.; Kuo, D. Z.; Coller, R.; Gaur, D. S.; Berry, J. G. Chronic Medication Use in Children Insured by Medicaid: A Multistate Retrospective Cohort Study. *Pediatrics*. **2019**, *143*. https://doi.org/10.1542/peds.2018-3397.
17. McPherson, T.; Fontane, P.; Iyengar, R.; Henderson, R. Utilization and Costs of Compounded Medications for Commercially Insured Patients, 2012-2013. *J. Manag. Care Spec. Pharm.* **2016**, *22*, 172–181. https://doi.org/10.18553/jmcp.2016.22.2.172.
18. Parrish II, R. H.; Cernak, I. Creating a Distinct Medication-Use System for Children at the Point of Care: The Time Is Now. *Pharmacy*. *2015*, *3*, 72–78. https://doi.org/10.3390/pharmacy3030072.
19. Blackmer, A. B.; Fox, D.; Arendt, D.; Phillips, K.; Feinstein, J. A. Perceived Versus Demonstrated Understanding of the Complex Medications of Medically Complex Children. *J. Pediatr. Pharmacol. Ther*. **2021**, *26*, 62–72. https://doi.org/10.5863/1551-6776-26.1.62.
20. Huth, K.; Vandecruys, P.; Orkin, J.; Patel, H. Medication Safety for Children with Medical Complexity. *Paediatr. Child Health*. **2020**, *25*, 473–473. https://doi.org/10.1093/pch/pxaa105.
21. Parrish II, R. H.; Casher, D.; van den Anker, J.; Benavides, S. Creating a Pharmacotherapy Collaborative Practice Network to Manage Medications for Children and Youth: A Population Health Perspective. *Children*. **2019**, *6*, 58. https://doi.org/10.3390/children6040058.
22. Aboneh, E. A.; Chui, M. A. Care Coordination, Medical Complexity, and Unmet Need for Prescription Medications among Children with Special Health Care Needs. *Res. Soc. Admin. Pharm*. **2017**, *13*, 524–529. https://doi.org/10.1016/j.sapharm.2016.05.043.
23. Feinstein, J. A.; Friedman, H.; Orth, L. E.; Feudtner, C.; Kempe, A.; Samay, S.; Blackmer, A. B. Complexity of Medication Regimens for Children With Neurological Impairment. *JAMA Netw. Open*. **2021**, *4*, e2122818. https://doi.org/10.1001/jamanetworkopen.2021.22818.
24. Shonna Yin, H.; Parker, R. M.; Sanders, L. M.; Dreyer, B. P.; Mendelsohn, A. L.; Bailey, S.; Patel, D. A.; Jimenez, J. J.; Kim, K. Y. A.; Jacobson, K.; Hedlund, L.; Smith, M. C. J.; Harris, L. M.; McFadden, T.; Wolf, M. S. Liquid Medication Errors and Dosing Tools: A Randomized Controlled Experiment. *Pediatrics.* **2016**, *138*. https://doi.org/10.1542/peds.2016-0357.
25. Parrish II, R. H.; Gilak, L.; Bohannon, D.; Emrick, S. P.; Serumaga, B.; Guharoy, R. Minimizing Medication Errors from Electronic Prescription Transmission—Digitizing Compounded Drug Preparations. *Pharmacy*. **2019**, *7*, 149. https://doi.org/10.3390/pharmacy7040149.
26. Solano, M.; Jeannin, M.; Anxionnat, R.; Vardanega, J.; Ridley, A.; Amsallem, D.; Limat, S.; Clairet, A.-L. Impact of Pharmacist Medication Review for Paediatric Patients: An Observational Study. *Int. J. Pharm. Pract*. **2022**. https://doi.org/10.1093/ijpp/riac037.
27. Marquez, C.; Thompson, R.; Feinstein, J. A.; Orth, L. E. Identifying Opportunities for Pediatric Medication Therapy Management in Children with Medical Complexity. *J. Am. Pharm. Assoc*. **2022**, *62*, 1587-1595.e3. https://doi.org/10.1016/j.japh.2022.04.005.
28. Parrish II, R. H.; van den Anker, J.; Benavides, S. Making Meaningful Improvements in Pharmacotherapy and Medication Management for Children and Youth—A Modest Proposal [editorial]. *Children*. **2019**, *6*, 111. https://doi.org/10.3390/children6100111.
29. Parrish II, R. H.; van den Anker, J. Toolkit for Population Health Initiatives Around the Globe Related to Collaborative Comprehensive Medication Management for Children and Youth. *Children*. **2019**, *6*, 57. https://doi.org/10.3390/children6040057.
30. Centers for Medicare & Medicaid Services. Hospital Readmissions Reduction Program (HRRP). Available online: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/Readmissions-Reduction-Program. Accessed 27 October 2022.
31. Berenson, R. A.; Paulus, R. A.; Kalman, N. S. Medicare's Readmissions-Reduction Program — A Positive Alternative. *New Eng. J. Med.* **2012**, *366*, 1364–1366. https://doi.org/10.1056/NEJMp1201268.

32. Bradley, E. H.; Curry, L.; Horwitz, L. I.; Sipsma, H.; Wang, Y.; Walsh, M. N.; Goldmann, D.; White, N.; Piña, I. L.; Krumholz, H. M. Hospital Strategies Associated With 30-Day Readmission Rates for Patients With Heart Failure. *Circ. Cardiovasc. Qual. Outcomes*. **2013**, *6*, 444–450. https://doi.org/10.1161/CIRCOUTCOMES.111.000101.
33. Bradley, E. H.; Sipsma, H.; Horwitz, L. I.; Ndumele, C. D.; Brewster, A. L.; Curry, L. A.; Krumholz, H. M. Hospital Strategy Uptake and Reductions in Unplanned Readmission Rates for Patients with Heart Failure: A Prospective Study. *J. Gen. Intern. Med*. **2015**, *30*, 605–611. https://doi.org/10.1007/s11606-014-3105-5.
34. Hernandez, A. F. Relationship Between Early Physician Follow-up and 30-Day Readmission Among Medicare Beneficiaries Hospitalized for Heart Failure. *JAMA*. **2010**, *303*, 1716. https://doi.org/10.1001/jama.2010.533.
35. Kociol, R. D.; Peterson, E. D.; Hammill, B. G.; Flynn, K. E.; Heidenreich, P. A.; Piña, I. L.; Lytle, B. L.; Albert, N. M.; Curtis, L. H.; Fonarow, G. C.; Hernandez, A. F. National Survey of Hospital Strategies to Reduce Heart Failure Readmissions. *Circ. Heart Fail*. **2012**, *5*, 680–687. https://doi.org/10.1161/CIRCHEARTFAILURE.112.967406.
36. Lyren, A.; Brilli, R.; Bird, M.; Lashutka, N.; Muething, S. Ohio Children's Hospitals' Solutions for Patient Safety. *J. Healthcare Qual*. **2016**, *38*, 213–222. https://doi.org/10.1111/jhq.12058.
37. Khan, A.; Nakamura, M. M.; Zaslavsky, A. M.; Jang, J.; Berry, J. G.; Feng, J. Y.; Schuster, M. A. Same-Hospital Readmission Rates as a Measure of Pediatric Quality of Care. *JAMA Pediatr*. **2015**, *169*, 905. https://doi.org/10.1001/jamapediatrics.2015.1129.
38. Bucholz, E. M.; Toomey, S. L.; Schuster, M. A. Trends in Pediatric Hospitalizations and Readmissions: 2010–2016. *Pediatrics.* **2019,** *143*. https://doi.org/10.1542/peds.2018-1958.
39. Cohen, E.; Kuo, D. Z.; Agrawal, R.; Berry, J. G.; Bhagat, S. K. M.; Simon, T. D.; Srivastava, R. Children With Medical Complexity: An Emerging Population for Clinical and Research Initiatives. *Pediatrics*. **2011**, *127*, 529–538. https://doi.org/10.1542/peds.2010-0910.
40. Cohen, E.; Patel, H. Responding to the Rising Number of Children Living with Complex Chronic Conditions. Can Med Assoc J 2014, 186 (16), 1199–1200. https://doi.org/10.1503/cmaj.141036.
41. Jurgens, V.; Spaeder, M. C.; Pavuluri, P.; Waldman, Z. Hospital Readmission in Children With Complex Chronic Conditions Discharged From Subacute Care. *Hosp. Pediatr*. **2014**, *4*, 153–158. https://doi.org/10.1542/hpeds.2013-0094.
42. Berry, J. G. Hospital Utilization and Characteristics of Patients Experiencing Recurrent Readmissions Within Children's Hospitals. *JAMA*. **2011**, *305*, 682. https://doi.org/10.1001/jama.2011.122.
43. Kun, S. S.; Edwards, J. D.; Davidson Ward, S. L.; Keens, T. G. Hospital Readmissions for Newly Discharged Pediatric Home Mechanical Ventilation Patients. *Pediatr. Pulmonol*. **2012**, *47*, 409–414. https://doi.org/10.1002/ppul.21536.
44. Easton-Carter, K.; Chapman, C.; Brien, J. Emergency Department Attendances Associated with Drug-Related Problems in Paediatrics. *J. Paediatr. Child Health*. **2003**, *39*, 124–129. https://doi.org/10.1046/j.1440-1754.2003.00103.x.
45. Posthumus, A. A. G.; Alingh, C. C. W.; Zwaan, C. C. M.; van Grootheest, K. K.; Hanff, L. L. M.; Witjes, B. B. C. M.; 't Jong, G. W.; de Hoog, M. Adverse Drug Reaction-Related Admissions in Paediatrics, a Prospective Single-Centre Study. *BMJ. Open*. **2012**, *2*, e000934. https://doi.org/10.1136/bmjopen-2012-000934.
46. Gallagher, R. M.; Mason, J. R.; Bird, K. A.; Kirkham, J. J.; Peak, M.; Williamson, P. R.; Nunn, A. J.; Turner, M. A.; Pirmohamed, M.; Smyth, R. L. Adverse Drug Reactions Causing Admission to a Paediatric Hospital. *PLoS One*. **2012**, *7*, e50127. https://doi.org/10.1371/journal.pone.0050127.
47. Kan, K.; Gupta, R.; Davis, M. M.; Heard-Garris, N.; Garfield, C. Adverse Experiences and Special Health Care Needs Among Children. *Matern. Child Health J.* **2020**, *24*, 552–560. https://doi.org/10.1007/s10995-020-02874-x.
48. Gholami, K.; Babaie, F.; Shalviri, G.; Javadi, M.; Faghihi, T. Pediatric Hospital Admission Due to Adverse Drug Reactions: Report from a Tertiary Center. *J. Res. Pharm. Pract*. **2015**, *4*, 212. https://doi.org/10.4103/2279-042X.167045.
49. Zandieh, S. O.; Goldmann, D. A.; Keohane, C. A.; Yoon, C.; Bates, D. W.; Kaushal, R. Risk Factors in Preventable Adverse Drug Events in Pediatric Outpatients. *J. Pediatr*. **2008**, *152*, 225–231. https://doi.org/10.1016/j.jpeds.2007.09.054.
50. Gore, R.; Chugh, P. K.; Tripathi, C. D.; Lhamo, Y.; Gautam, S. Pediatric Off-Label and Unlicensed Drug Use and Its Implications. *Curr. Clin. Pharmacol*. **2017**, *12*. https://doi.org/10.2174/1574884712666170317161935.
51. Binson, G.; Sanchez, C.; Waton, K.; Chanat, A.; di Maio, M.; Beuzit, K.; Dupuis, A. Accuracy of Dose Administered to Children Using Off-Labelled or Unlicensed Oral Dosage Forms. *Pharmaceutics*. **2021**, *13*. https://doi.org/10.3390/pharmaceutics13071014.
52. Stone, B. L.; Boehme, S.; Mundorff, M. B.; Maloney, C. G.; Srivastava, R. Hospital Admission Medication Reconciliation in Medically Complex Children: An Observational Study. *Arch. Dis. Child*. **2009**. https://doi.org/10.1136/adc.2009.167528.
53. Kaushal, R. Medication Errors and Adverse Drug Events in Pediatric Inpatients. *JAMA*. **2001**, *285*, 2114. https://doi.org/10.1001/jama.285.16.2114.
54. Coffey, M.; Mack, L.; Streitenberger, K.; Bishara, T.; de Faveri, L.; Matlow, A. Prevalence and Clinical Significance of Medication Discrepancies at Pediatric Hospital Admission. *Acad. Pediatr*. **2009**, *9*, 360-365.e1. https://doi.org/10.1016/j.acap.2009.04.007.
55. Holdsworth, M. T.; Fichtl, R. E.; Behta, M.; Raisch, D. W.; Mendez-Rico, E.; Adams, A.; Greifer, M.; Bostwick, S.; Greenwald, B. M. Incidence and Impact of Adverse Drug Events in Pediatric Inpatients. *Arch. Pediatr. Adolesc. Med*. **2003**, *157*, 60. https://doi.org/10.1001/archpedi.157.1.60.
56. Slonim, A. D.; LaFleur, B. J.; Ahmed, W.; Joseph, J. G. Hospital-Reported Medical Errors in Children. *Pediatrics*. **2003**, *111*, 617–621. https://doi.org/10.1542/peds.111.3.617.
57. Munn, Z.; Barker, T.H.; Moola, S.; Tufanaru, C.; Stern, C.; McArthur, A.; Stephenson, M.; Aromataris, E. Methodological quality of case series studies: an introduction to the JBI critical appraisal tool. *JBI Evid. Synth*. **2020**, *18*, 2127-2133. https://doi.org/10.11124/JBISRIR-D-19-00099.
58. Cipolle, R.J.; Strand, L.M.; Morley, P.C. Chapter 5. Drug Therapy Problems. In: Cipolle, R.J., Strand, L.M., Morley, P.C. (eds.) *Pharmaceutical Care Practice: The Patient-Centered Approach to Medication Management Services*, 3e. New York: McGraw Hill; 2012. Available online: https://accesspharmacy.mhmedical.com/content.aspx?bookid=491&sectionid=39674905. Accessed 4 November 2022.
59. Ranieri, M. Handbook of Drug Administration Via Enteral Feeding Tubes, 3rd Edition. *Am. J. Health-Syst. Pharm.* **2015,** *72*, 1239–1240. https://doi.org/10.1093/ajhp/72.14.1239a.
60. McIntyre, C. M.; Monk, H. M. Medication Absorption Considerations in Patients with Postpyloric Enteral Feeding Tubes. *Am. J. Health-Syst. Pharm*. **2014**, *71*, 549–556. https://doi.org/10.2146/ajhp130597.

61. Volpi-Abadie, J.; Kaye, A. M.; Kaye, A. D. Serotonin Syndrome. *Ochsner J.* **2013**, *13*, 533–540.
62. Huth, K.; Vandecruys, P.; Orkin, J.; Patel, H. Medication Safety for Children with Medical Complexity. *Paediatr. Child Health*. **2020**, *25*, 473–473. https://doi.org/10.1093/pch/pxaa105.
63. Rieder, M. Adverse Drug Reactions in Children: Pediatric Pharmacy and Drug Safety. *J. Pediatr. Pharmacol. Ther.* **2019**, *24*, 4–9. https://doi.org/10.5863/1551-6776-24.1.4.
64. The Use of Fluoride in Infants and Children. *Paediatr. Child Health*. **2002**, *7*, 569–582. https://doi.org/10.1093/pch/7.8.569.
65. Benavides, S.; Madzhidova, S.; Hernandez, A.; Le, T.; Palma, S.; Stephen, S. Establishment of Pediatric Medication Therapy Management: A Proposed Model. *Pharmacy*. **2016**, *4*, 5. https://doi.org/10.3390/pharmacy4010005.
66. Lampkin, S. J.; Gildon, B.; Benavides, S.; Walls, K.; Briars, L. Considerations for Providing Ambulatory Pharmacy Services for Pediatric Patients. *J. Pediatr. Pharmacol. Ther.* **2018**, *23*, 4–17. https://doi.org/10.5863/1551-6776-23.1.4.
67. Feinstein, J. A.; Orth, L. E. Making Polypharmacy Safer for Children with Medical Complexity. *J. Pediatr.* **2022**. https://doi.org/10.1016/j.jpeds.2022.10.012.
68. Burrus, T.E.; Vogt, H.; Pettit, R.S. Impact of a pharmacy technician and pharmacist on time to inhaled tobramycin therapy in a pediatric cystic fibrosis clinic. *Pediatr Pulmonol*. **2021**, *56*, 2861-2867. doi: 10.1002/ppul.25554.
69. Kuhn, C.; Groves, B.K.; Kaczor, C.; Sebastian, S.; Ramtekkar, U.; Nowack, J.; Toth, C.; Valenti, O.; Gowda, C. Pharmacist Involvement in Population Health Management for a Pediatric Managed Medicaid Accountable Care Organization. *Children (Basel)*. **2019**, *6*:82. https://doi.org/10.3390/children6070082.