In this issue: POCT – making the point

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POCT: an inherently ideal tool in pediatric laboratory medicine

Siobhan Wilson[a,b], Mary Kathryn Bohn[a,b], Khosrow Adeli[a,b]

[a] *Division of Clinical Biochemistry, Pediatric Laboratory Medicine, The Hospital for Sick Children, Toronto, Ontario, Canada*

[b] *Department of Laboratory Medicine & Pathobiology, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada*

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Corresponding author:
Khosrow Adeli
Pediatric Laboratory Medicine
The Hospital for Sick Children
555 University Avenue
Toronto, ON, M5G 1X8
Canada
Phone: 416-813-8682 ext. 208682
E-mail: khosrow.adeli@sickkids.ca

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ABSTRACT

Point of care testing (POCT) is important in the provision of timely laboratory test results and continues to gain specific appreciation in the setting of pediatric healthcare. POCT platforms offer several advantages compared to central laboratory testing, including improved clinical outcomes, reduced time to diagnosis, length of stay, and blood volume requirements, as well as increased accessibility. These advantages are most pronounced in acute care settings such as pediatric emergency departments, intensive care units, and in remote settings, wherein rapid patient assessment and prognostication is essential to patient outcomes. The current review provides an overview and critical discussion of the evidence supporting clinical implementation of POCT systems in pediatric clinical decision-making, including but not limited to the diagnosis of viral and bacterial infection, identification of critical glucose and electrolyte dysregulation, and prognostication of post-operative inpatients.

Important considerations for test result reporting and interpretation are also discussed, including analytical concordance between POCT systems and central laboratory analyzers as well as availability of pediatric reference intervals for key analytes on POCT systems. Notably, a paucity of evidence-based pediatric reference intervals for test interpretation for critical care parameters on POCT platforms is highlighted, warranting further study and unique consideration prior to clinical implementation.

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BACKGROUND

Point of care testing (POCT) refers to laboratory testing performed in near-patient settings as opposed to the central laboratory. Narrowing the clinical-laboratory interface, POCT has become increasingly important in the provision of accurate and timely laboratory test results in both acute and remote patient settings. Longer turnaround-time (TAT) poses a significant barrier to rapid test interpretation, lengthening the time to appropriate clinical decision-making with known patient impact (1). Several reports have demonstrated both clinical and economic benefits to the implementation of POCT systems, including reduced TAT, length of stay, mortality, and enhanced cost effectiveness in a variety of clinical settings (2). While clinical laboratories were initially hesitant to adopt such technology due to concerns regarding analytical performance, increasing data suggests improved analytical concordance between common laboratory-based instruments and newer POCT platforms for several analytes, providing further support to their reliability for direct clinical implementation. Recent developments in POCT platforms have also expanded available assay menus to include key chemistry and immunoassay parameters, such as troponin and creatinine, further increasing their potential clinical utility.

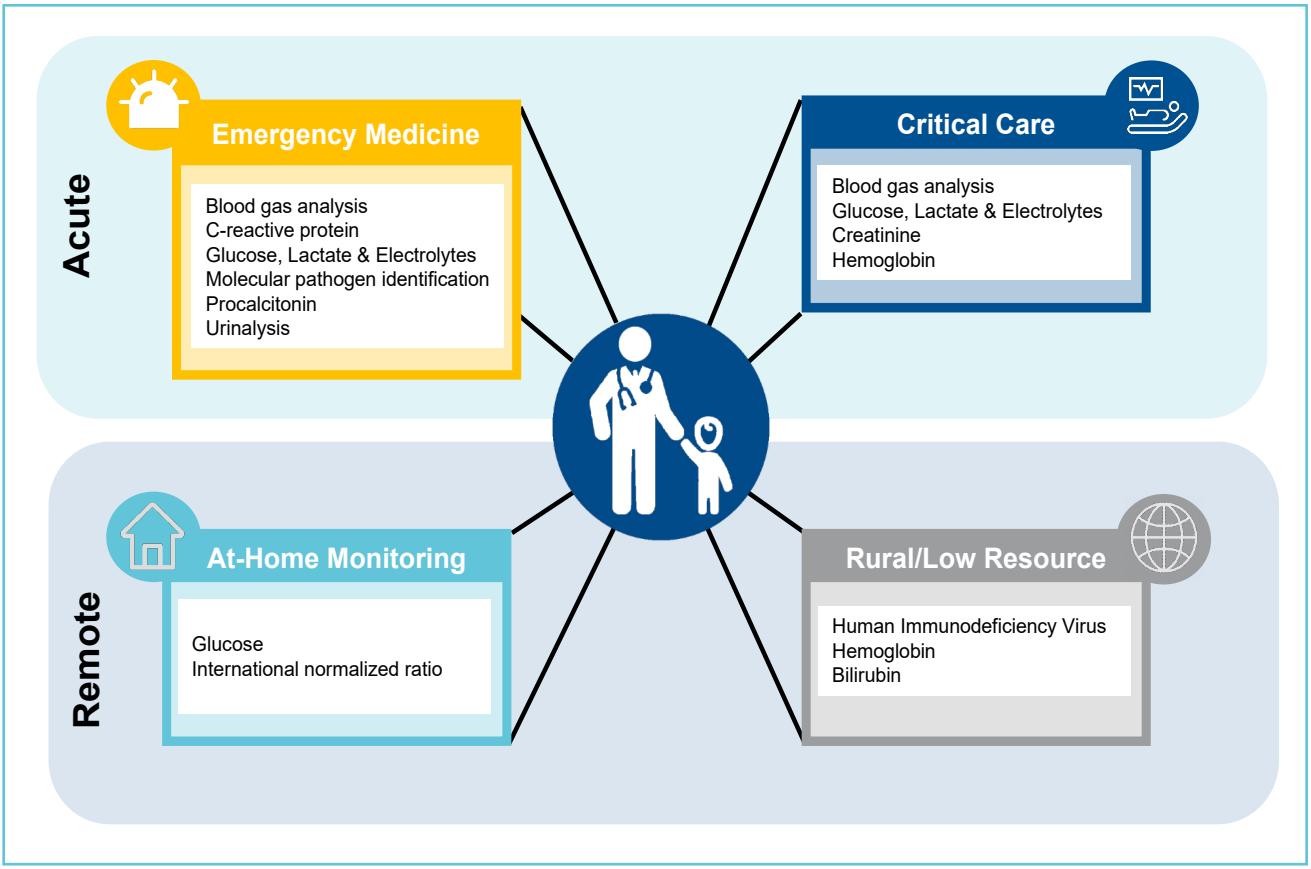
The clinical implementation of POCT platforms in pediatric institutions presents unique advantages as well, including smaller sample volume requirements. This is particularly true for emergency and critical care departments wherein rapid patient assessment and prognostication is essential to patient outcome. In this review, we will discuss the current state of POCT in pediatric healthcare centres, including its application in emergency, intensive care, and remote settings, and discuss unique considerations required for test interpretation (e.g. pediatric reference intervals) on POCT systems in children and adolescents (Figure 1).

ACUTE SETTINGS

Pediatric emergency medicine

Rapid assessment and diagnosis of acute conditions is essential in emergency departments (EDs) to ensure appropriate triage, timely intervention, and to prevent unnecessary hospital admission. As POCT systems evolve to include more complex testing menus, their value in pediatric emergency medicine is being increasingly recognized and supported. Fever is one of the main clinical presentations requiring consultation in pediatric emergency medicine. In febrile pediatric patients, it is essential to rapidly diagnose the infection source (e.g. bacterial or viral) as well as identify patients at high risk of serious bacterial infection. C-reactive protein (CRP), a positive acute phase reactant, is a valuable biomarker in the rapid identification of inflammatory processes. While most commonly measured by laboratory-based chemistry analyzers, few studies have evaluated the clinical and economic impacts of implementing POC CRP testing in pediatric EDs. In a study of 68 febrile pediatric patients, the availability of real-time POC CRP results resulted in a significant drop in ED consultation and medical intervention, without significant change in patient outcome (3).

Figure 1 Clinical utility of POCT in pediatric healthcare settings



Additionally, in a large prospective study of 283 well-appearing febrile infants, strong analytical concordance was observed between POC QuikRead go® and laboratory-based Abbott ARCHITECT platforms (4), resulting in accelerated diagnostic management of febrile patients, optimized ED patient flow, and substantially reduced length of stay (4). These findings are supported by other studies reporting decreased length of stay (5) as well as reduction of immediate antibiotic prescribing post-implementation of POC CRP testing (6,7). In addition to CRP, procalcitonin (PCT), a 116-amino acid protein produced by parafollicular cells, has gained considerable appreciation in the literature as an ideal marker of bacterial infection due to its rapid concentration peak post-endotoxin exposure (8). Recent evidence supports POC PCT testing in initial ED assessment of young febrile infants to improve early recognition of bacterial infection (9,10). However, its advantage over CRP in a POCT setting is still unclear and further research is warranted. In addition to PCT and CRP, POCT for direct molecular pathogen identification, including respiratory syncytial virus (RSV) and influenza A/B, has become increasingly adopted in pediatric EDs. Several reports suggest excellent analytical and clinical performance of both PCR and antigen-based POC assays for molecular pathogen identification in pediatric settings. Side-by-side comparisons of antigen-based respiratory syncytial virus (RSV) and influenza A/B assays relative to laboratory-based nucleic acid amplification tests have reported excellent analytical concordance in pediatric ED settings (NPV>90%, PPV>89%) (11). Subsequent clinical advantages have been observed post-implementation, including reduced length of stay (12), improved

hospital workflow (13,14), cost effectiveness (15), as well as decreased laboratory investigations and antibiotic/antiviral ordering in peak flu season (16), providing further rationale for clinical implementation.

Finally, it is important to note that urinalysis and blood gas analysis also play important roles in pediatric ED assessment. Rapid testing of blood gases, glucose, lactate, ionized calcium, and electrolytes on POCT systems is an integral component to the assessment of children presenting to the ED with acid-base disturbances, tissue damage, and dyselectrolytemias. Indeed, the implementation of POCT blood gas analyzers in EDs has been shown to shorten the laboratory process, allowing for quicker discharge with proper training and education (17). Dipstick and automated urinalysis at the POC have also demonstrated significant value in the identification of urinary tract infection (UTI), particularly in young children (18–20). However, rapid identification of pyuria by urine dipstick in children has been correlated to unnecessary antibiotic exposure, suggesting diagnostic accuracy of urine dipstick is suboptimal and waiting for culture results should be considered prior to antibiotic prescription (21). Identification of hematuria via urinalysis at the POC has also demonstrated clinical value in the assessment of kidney disease as well as urinary or renal blockages/obstructions in pediatric ED settings (22).

Pediatric critical care units

While increasing implementation of POCT systems in pediatric EDs is evident, the value of POCT in pediatrics is most clearly demonstrated in intensive care units (ICU), wherein rapid TAT and test result interpretation is integral to appropriate patient diagnosis and management. Particular analytes of interest in this clinical context include blood gases, glucose, and electrolytes, as discussed below.

Blood gas analysis is often used as a metric of overall metabolic function and health, wherein acid-base disturbances are common among critically ill patients. As frequent blood gas and pH assessments are essential for patient management in pediatric ICUs (PICUs), POCT provides an ideal service to ensure rapid result reporting and interpretation. Several analytical and clinical evaluations of POC blood gas instruments in ICU departments have been reported. Specifically, analytical evaluations of the i-STAT (Abbott Diagnostics) and epoc (Siemens Healthineers) systems have demonstrated excellent concordance with the central laboratory for main blood gas parameters (pH, pCO2, and pO2; $r>0.99$) in pediatric settings (23,24). Several clinical benefits have also been observed post-implementation, including improved cost-effectiveness (25), quality of care (25), and significant reductions in red blood cell transfusions in low-birth weight infants, which are often required due to phlebotomy-induced anemia (26). It is also important to note that blood gas analyzers can be prone to interferences. The use of syringes with minimal liquid heparin is recommended to mitigate this effect, although more research is required to compare analytical performance when using liquid and dry balanced heparin syringes (27).

Glucose dysregulation is very common in critically ill patients and is associated with adverse outcomes, including organ failure and mortality (28). This is particularly important for patients in the neonatal intensive care unit (NICU) wherein glucose dysregulation is highly prevalent and close monitoring is required. Indeed, the neonatal period is characterized by a normative phase of transitional hypoglycemia; however, prolonged periods of critically low blood glucose can induce serious complications, such as cerebral ischemia, seizures, long-term neurodevelopmental damage, and mortality (29,30). As hypoglycemia often presents asymptomatically, laboratory-driven investigation is critical

to prevent unnecessary and adverse outcomes. Consequently, the American Academy of Pediatrics recommends serial blood glucose monitoring in both symptomatic and asymptomatic neonates at increased risk of glucose dysregulation. In addition, hyperglycemia is common in ICU patients, resultant primarily from physiologic stress caused by surgery, respiratory distress, and/or sepsis. Numerous studies have therefore assessed potential clinical advantages of implementing POCT systems for glucose measurements in NICUs and PICUs (31–33). In addition, studies have also sought to assess the analytical performance of POCT devices. For example, modern POCT devices, such as the StatStrip (Nova Biomedical) (31) and iSTAT (Abbott Diagnostics) (33,34), have demonstrated excellent concordance with central laboratory blood glucose assessments in critical care settings. Despite reported concordance, it is important to consider specimen type in test interpretation (e.g. capillary/venous whole blood, plasma, serum), particularly when both POC and laboratory-based analyzers are being used in patient monitoring.

Electrolytes are vital to maintaining whole-body homeostasis required for regular metabolic functioning. Due to a number of inducing factors, such as chronic disease (e.g. respiratory disease, renal failure) (35), inappropriate intravenous administration (36), acute critical conditions (i.e. sepsis, severe burns, trauma, brain damage, heart failure) (37), or major surgery (38), patients in the ICU often present with electrolyte imbalances. This dysregulated state often goes undetected and has been associated with a five-fold increased risk of mortality in such patients (35). Given the high prevalence and potential clinical severity of electrolyte abnormalities, POCT offers unique advantages in mitigating avoidable poor outcomes in ICU patients, by reducing TAT and subsequently leading to more rapid test interpretation. Indeed, several studies have evaluated the analytical accuracy of POC analyzers compared to central laboratory systems in electrolyte assessment. For example, acceptable clinical concordance between both the i-STAT (Abbott Laboratories; (34)) and Xpress analyzer (Nova Biomedical; (39)) with central laboratory instruments have been observed. However, other reports have demonstrated a significant bias in key electrolytes reported at the POC in ICUs (40,41). Several factors may contribute to the disparities observed in POC versus central laboratory testing, such as differing sample matrices (i.e. whole blood versus serum/plasma) and interferences in POC devices (e.g. heparin). Further research is needed to evaluate analytical performance of new instruments as they are developed. Importantly, no studies have assessed the clinical impact of electrolyte POCT in NICU and PICU patients; thus, this warrants further investigation to delineate their role in these clinical settings.

Peri- and post-operative patient management

POC instruments have also demonstrated clinical value in the peri- and post-operative setting, particularly in the measurement of creatinine, lactate, and hemoglobin. It is well appreciated that post-operative pediatric patients undergoing major cardiac surgery are at disproportionately higher risk of developing acute kidney injury (AKI), especially those on cardiopulmonary bypass (42). Recent developments in POCT have enabled measurement of known AKI marker, creatinine, with anticipated value in this setting. Few reports have assessed the analytical and clinical performance of POC creatinine testing in post-operative patients. In a study of 498 infants admitted to the PICU following cardiac surgery, Kimura et al. observed an excellent correlation between ABL800 (Radiometer) POCT platform (whole blood) and a central laboratory (serum) analyzer (r=0.968) (43). However, the clinical significance of creatinine measured at the POC

relative to laboratory-based settings was not conclusive. Specifically, despite encouraging analytical concordance, the incidence of AKI diagnosis among patients differed significantly across platforms, with POCT demonstrating significantly higher identification rates. Differential clinical outcomes may be partially due to improved detection of abnormal creatinine levels at the POC as a result of increased test frequency as compared to the central laboratory. However, with repeated testing, there is also an increased risk of misidentifying elevated creatinine (43). As Kimura et al. were the first to assess creatinine POCT in pediatrics, future research is warranted to elucidate both the analytical performance and clinical utility in this setting. In addition to creatinine, lactate assessment at the POC has demonstrated value as a predictor of morbidity and mortality in post-operative pediatric patients (44). Increasing reports have highlighted particular value following congenital heart surgery (CGS), wherein tissue oxygen delivery is compromised and often complicated by liver and renal dysfunction (45). Serial lactate testing is thus considered standard practice following CGS, and is often performed on POCT systems due to lower TAT and demonstrated analytical concordance with laboratory-based analyzers (46,47). Additionally, post-operative goal-directed therapy for blood lactate assessment via POCT resulted in a significant drop in overall mortality in NICU patients (48). However, it is important to note that some studies evaluating POC lactate testing have demonstrated reduced reproducibility at low concentrations (47) and systemic biases relative to the central laboratory (46,47). Clinical laboratories should ensure to monitor POC lactate performance relative to central laboratory testing, particularly if both are being used for patient assessment. Finally, hemoglobin is frequently ordered in the perioperative setting (49) as anemia is extremely common herein and is associated with increased complications, including mortality (50). To ensure timely clinical decision-making regarding potential transfusions, several studies have evaluated the analytical performance of hemoglobin testing on POCT systems in the peri-operative setting. A formative study by Spielmann et al. evaluated the analytical performance of arterial hemoglobin measurement across several POCT platforms in a cohort of pediatric patients undergoing major surgery. Specifically, blood was drawn from an arterial catheter several times during surgery and subsequently assessed on four POCT platforms (GEM Premier 3000, ABL 800, GEM OPL, HemoCue B-Hemoglobin) and compared to a central laboratory analyzer (Sysmex XE 2100) (51). All POCT devices demonstrated excellent concordance ($r>0.95$) and minimal bias (<1%) with respect to the reference method (51). These findings are supported by other studies assessing the accuracy, precision, and practicality of capillary hemoglobin measurement on three POC devices (capillary hematocrit, HemoCue Hb210+, and i-STAT,) relative to central laboratory measurement, demonstrating acceptable concordance ($r>0.91$) (52). Reported analytical comparability is encouraging, especially given differences in analytical methodology across testing platforms. Specifically, most POCT platforms indirectly calculate hemoglobin levels based on hematocrit measurement, whereas central laboratory analyzers often employ flow cytometry. Importantly, no studies have assessed the clinical advantages of implementing POC hemoglobin testing in this setting and thus further clinical evaluations are warranted.

REMOTE SETTINGS

In addition to the assessment of critical conditions in emergent settings, at-home monitoring of chronic conditions and patient assessment in remote or rural settings through POCT systems presents unique advantages in the pediatric population.

At-home monitoring of chronic conditions

One key example of at-home use of POCT systems is glucose management in diabetic patients. User-friendly glucometers were among the first POCT devices developed and approved by regulatory bodies to monitor diabetic patients outside of the hospital. While it was previously recommended by the National Institute for Health and Care Excellence that diabetic patients undergo 4–10 finger prick measurements per day to adequately manage their condition (53), the development of continuous glucose monitors (CGM) has revolutionized glucose management. These systems exploit various physiochemical principles (i.e. glucose-oxidase, fluorescence, skin dielectric properties, etc.) to provide real-time measurements every 1–5 minutes. Numerous companies have developed wearable, minimally invasive CGM devices, which can be worn for up to several days to weeks at a time: Dexcom (G4 Platinum, G5 Mobile), Medtronic (Enlite Sensor, Guardian Sensor 3), Abbott (Navigator II, FreeStyle Libre), and Senseonics (Eversense). Several studies have evaluated the analytical accuracy of CGM instruments compared to the central laboratory, and have demonstrated generally good concordance (54,55), underscoring their unique value. However, the role of the clinical laboratory in monitoring and reporting glucose values as determined by CGM is unclear and warrants further consideration. Another common application of at-home POCT in pediatrics is international normalized ratio (INR) monitoring in patients who require long-term oral anticoagulation (e.g. warfarin) therapy. Warfarin is the preferred anticoagulant used in pediatrics and has become increasingly important due to increased survival of children with severe conditions at higher risk of thrombolytic events (e.g. congenital heart disease). INR monitoring requires daily laboratory testing and thus POCT offers an opportunity for pediatric patients in remote regions to adhere to a proper monitoring schedule. Few studies have assessed the clinical and analytical performance of POC INR testing. In terms of analytical performance, one study evaluating the CoaguChek XS system reported high analytical concordant relative to a central analyzer (r =0.95) (56). Additional clinical evaluations have suggested this system to be suitable for pediatric assessment (57), observing increased savings in both time (>1 hour) and cost per INR test, compared to traditional care (58).

Rural or low-resource settings

Another emerging application of POCT is rural settings where a central laboratory is inaccessible. For example, early infant diagnosis of human immunodeficiency virus (HIV) is particularly challenging in rural areas of sub-Saharan Africa, where infection rates are high and centralized testing can lead to substantial delays in diagnosis and treatment (59). Early intervention can be critical in reducing HIV-associated morbidity and mortality, and POCT has demonstrated value in this regard (59–61). In addition, the prevalence of sickle cell disease (SCD) is an ongoing concern in countries without access to newborn screening programs, wherein undetected SCD is strongly associated with under-five mortality (62). POCT may offer a unique advantage in these regions. Indeed, studies that have implemented POCT for the detection of sickle hemoglobin are encouraging. Excellent sensitivities (>93%) and specificities (>99%) using the HemoTypeSC POC device in children screened for SCA have been reported (63,64). Additional large-scale studies are needed to confirm the clinical advantage of POCT implementation in this scenario. Lastly, newborn infants are also at an increased risk for jaundice, which is characterized by increased bilirubin concentrations (65). Timely diagnosis of newborn jaundice is critical and a routine component of neonatal assessment in modern tertiary hospitals. Left untreated, newborn jaundice can result in neurological damage and death

in severe cases. Several POCT systems have recently been designed to measure bilirubin and have demonstrated excellent concordance with the central laboratory (66,67), thereby offering immense clinical potential in remote settings.

UNIQUE INTERPRETATIVE CONSIDERATIONS IN PEDIATRIC POCT

Given the clinical indications discussed above, it is clear that POCT provides clinical value in both acute and remote pediatric settings, ensuring timely test result reporting. However, while studies suggest good to excellent analytical performance of these devices as compared to central laboratory analyzers, an equally important consideration is test result interpretation. Reference intervals, defined as the 2.5th and 97.5th percentiles derived from a reference population, are important health-associated benchmarks that are used to flag abnormal laboratory test results and alert clinicians of the potential need for follow-up and/or treatment. Unfortunately, while most analytical platforms (including POCT devices) provide reference intervals for test interpretation in their package insert, they are primarily based on adult populations and do not include pediatric recommendations. This is likely resultant from challenges encountered in pediatric reference interval establishment, including extensive resources required for recruitment, higher sample size needed to adequately reflect age- and sex-specific changes during growth and development, as well as ethical considerations limiting resampling opportunities (68). These unique challenges have often led to the implementation of adult-based reference intervals for pediatric test result interpretation, which may cause significant and adverse clinical outcomes. To address this evidence gap, several initiatives have been developed, including the Canadian Laboratory Initiative on Pediatric Reference Intervals (CALIPER) (69), the Harmonising Age Pathology Parameters in Kids (70), Children's Health Improvement through Laboratory Diagnostics (71), KiGGs study (72), and Lifestyle of Our Kids program (73). However, most of these initiatives focus on biochemical and immunochemical assays available on central laboratory analyzers. Establishment of pediatric reference intervals on POCT systems is further complicated due to rapid pre-analytical requirements, preventing specimen storage and batch testing. This has led to an immense gap in the literature with practically no studies developing reference intervals on POCT systems for pediatrics, despite their growing clinical value. Future pediatric reference interval studies in this area should focus on important covariates, such as age, sex, and specimen type. Importantly, as discussed above, unique physiological dynamics influence biochemical markers (e.g. glucose), particularly in early life, requiring close consideration of key covariates and age-specific interpretation. This further emphasizes the necessity for robust, evidence-based reference intervals that adequately capture dynamic changes in analyte concentration that occur throughout pediatric growth and development. Recently, CALIPER has expanded the utility of their database to include critical care parameters on a common POCT system (Radiometer ABL90 FLEX Plus) (74) and plans to continue completing studies on alternate POCT platforms to close this evidence gap. Taken together, clinical laboratories and clinicians should recognize the limited evidence surrounding pediatric normative values for key parameters on POCT systems and the potential impact on clinical decision-making.

Another important distinction of note is that some parameters commonly assessed in acute care on POCT systems (e.g. glucose, electrolytes, pH) have associated critical values or cut-offs to define extremely abnormal values warranting immediate follow-up and clinical action. Unfortunately, these decisionlimits are also commonly based on clinical evidence in adult populations (75). New studies are needed to

develop evidence-based reference intervals and critical values for POCT platforms in children and adolescents as implementation and usage of POCT devices continues to grow in pediatric settings.

CONCLUSION

In conclusion, current POCT systems offer a unique set of advantages in pediatric healthcare provision, particularly in acute and remote settings. Evidence to date supports several key benefits to patient care, including reduced length of stay, improved time to diagnosis, improved acute condition outcomes, improved condition management, and reduced cost of hospital admission. With proper education and training, additional administrative and economic advantages have also been reported, including improved staff satisfaction and clinical workflow efficiency. However, not all POCT systems are created equal and differences between POCT systems and central laboratory analyzers continue to be reported and may sometimes require device-specific test interpretation. In addition, pediatric reference interval studies are lacking for POCT systems, compromising the accuracy and standard of test result interpretation in infants, children, and adolescents. Further studies are needed to establish pediatric reference intervals and/or critical values as new POCT systems are developed. Taken together, while implementation of POCT systems in emergency, critical care, and remote settings has demonstrated major clinical value in pediatrics, close consideration of their analytical (e.g. comparison to central laboratory) and post-analytical (e.g. test result interpretation) requirements is needed prior to clinical implementation.

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