Retrospective review of antimicrobial use for gastroschisis patients in Kigali, Rwanda: can improved stewardship reduce late inpatient deaths?

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Abstract

Purpose

Gastroschisis mortality is 75–100% in low-resource settings. In Rwanda, late deaths are often due to sepsis. We aimed to understand the effect of antimicrobial use on survival.

Methods

We conducted a retrospective review of gastroschisis patients at a tertiary hospital in Kigali, Rwanda between January 2016—June 2019. Demographics, antimicrobial use, culture data, and outcome were abstracted. Descriptive and univariate analyses were conducted to assess factors associated with improved survival.

Results

Among 92 gastroschisis patients, mortality was 77%(n = 71); 23%(n = 21) died within 48 hours. 98%(n = 90) of patients received antibiotics on arrival. Positive blood cultures were obtained in 41%(n = 38). Patients spent 86%(SD = 20%) of hospital stay on antibiotics and 38%(n = 35) received second-line agents. There was no difference in age at arrival, birth weight, gestational age, silo complications, or antimicrobial selection between survivors and non-survivors. Late death patients spent more total hospital days and post-abdominal closure days on antibiotics ($p < 0.001$) compared to survivors. There was no difference in the proportion of hospital stay on second-line antibiotics ($p = 0.1$).

Conclusion

Frequent late deaths due to sepsis, prolonged antibiotic courses, and regular use of second-line antibiotic agents were identified in this retrospective cohort of gastroschisis patients. Future studies are needed to evaluate antimicrobial resistance in Rwanda.

Introduction

Global under-five mortality decreased by more than 50% between 1990 and 2015 as a result of the Millennium Development Goals, a set of public health priorities and targets established by the United Nations [1]. Unfortunately, neonates—infants less than 28 days old—did not experience the same global health successes. Neonatal deaths now account for nearly half (47%) of deaths among children under age five [2]. While infection, prematurity and birth asphyxia represent the leading causes of neonatal mortality, surgically treatable conditions contribute significantly [2]. In fact, congenital anomalies (which often require surgical management) are estimated to be the 5th leading cause of under-five mortality, up from the 6th leading cause in 2005 [3, 4]. Furthermore, disparities in global surgical outcomes are extreme

in the neonatal population. As an example, gastroschisis—a common congenital abdominal wall defect—has a less than 4% mortality rate in high-income countries, but 75–100% mortality rate in low- and middle-income countries (LMICs) [5].

Previously published work concerning gastroschisis outcomes in Rwanda demonstrated an improvement in survival from 0–22% within the last five years [6]. Such a marked improvement in survival was closely linked to the establishment of a functional pediatric surgery service in 2017 and rapid development of capacity for pediatric critical care at The University Teaching Hospital of Kigali (Centre Hospitalier Universitaire de Kigali [CHUK]). In a retrospective analysis of all gastroschisis patients admitted to CHUK from 2016–2019, most neonates arrived within 24 hours of birth and the majority (80%) survived the initial 48 hours after admission. However, more than half of patients who survived the initial 48 hours died prior to hospital discharge (late deaths) [6]. The precise etiologies for late deaths are not completely understood, but clinical experience among Rwandan experts suggest that sepsis and antimicrobial resistance (AMR) are the driving factors.

Globally, sepsis is known to be the most common cause of death in surgical neonates and this problem is exacerbated by AMR [7–9]. Across all age groups in sub-Saharan Africa, 23.7 per 100,000 deaths are attributable to AMR [10]. Specifically in Rwanda, data available to guide antimicrobial stewardship is sparse, but suggests increasing multidrug resistance amongst gram-negative bacteria, which are frequently encountered with gastrointestinal pathologies, such as gastroschisis [11–14]. Sepsis diagnosis and management, therefore, not only arrival at a tertiary care center, are critical to further improvement in gastroschisis outcomes. In this study, we seek to understand patterns of antimicrobial use for gastroschisis patients at a single tertiary hospital in Kigali, Rwanda. In doing so, we aim to identify modifiable factors to minimize late deaths in gastroschisis patients in Rwanda.

Materials And Methods

Setting and Context:

CHUK is a 520-bed public, tertiary care hospital in Rwanda’s capital city. It is one of four referral hospitals in the country and the only hospital offering comprehensive pediatric surgical and anesthesia services for Rwanda’s 12.2 million population [15]. In addition, CHUK has a 3-bed PICU with availability of neonatal ventilation and a high-dependency unit. Due to CHUK’s large catchment area, the hospital receives a significant number of outborn neonates (born outside of CHUK’s facility), who are transferred in by ambulance for surgical evaluation. Patients transferred to CHUK with gastroschisis are received in the pediatric emergency room and co-managed by a team of pediatricians, pediatric surgeons, pediatrics residents, and general surgery residents. Preformed silos (PFS) are applied in the emergency room and simple gastroschisis patients (without atresia, ischemia, volvulus, or perforation) routinely undergo staged reduction and bedside closure [16].

Study Population and Outcomes

We completed a single-center, retrospective review of all gastroschisis patients admitted to the CHUK between January 2016 and June 2019 [6]. Reporting of this study was done in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist [17]. Demographic data included birth location, sex, birth weight, gestational age, and age at admission. The outcomes of interest were 1) survival to hospital discharge, 2) impact of blood culture results on survival outcomes, and 3) comparison of patterns of antimicrobial usage between survivors and non-survivors, including specific antimicrobial regimens, proportion of hospital stay on antibiotics, and proportion of post-abdominal closure stay on antibiotics.

Data Collection

Patients were identified from hospital registries and their medical charts were obtained from hospital archives. Data was extracted and entered into a secure REDCap database. Abstracted data included demographics, referral history, admission interventions, daily antimicrobial usage, operative details, in-hospital complications, length of stay, and mortality. All data were de-identified and stored on an encrypted University of Florida server. Further methodological details are available in previously published work [6]. This project was approved by the CHUK Ethics Committee and University of Florida Institutional Review Board.

Data Analysis:

Descriptive and univariate analyses were conducted with primary outcome being survival to hospital discharge. Fisher's exact test was used to compare groups on categorical outcomes. All analyses were performed using R statistical software package (V.4.0.2, The R Foundation for Statistical Computing).

Results

92 patients presented with gastroschisis during our study period. The characteristics of patients are described in Table 1. Sex was evenly distributed with 47 (51.1%) females and 45 (48.9%) males. Mean gestational age was 36.0 weeks (standard deviation (SD) = 2.2). Mean age at arrival was 0.6 days (SD = 0.75), and mean length of stay was 16.1 days (SD = 15.8) overall, 28.3 days (SD = 10.4) for survivors.

Table 1
Patient Characteristics

Female, *n (%)*	**47 (51.1)**
Male, *n (%)*	45 (48.9)
Age at presentation *(SD), days*	0.6 (0.75)
Birth location, *n (%)*	
District Hospital	50 (54.9)
Health Center	34 (37.4)
Other	8 (8.7)
Birth weight *(SD), kg*	2.3 (0.45)
Premature, *n (%)*	31 (33.7)
Simple gastroschisis	75 (81.5)
Complicated gastroschisis	17 (18.5)

21 patients (22.8%) survived to hospital discharge. Among the 71 (77.2%) in-hospital deaths, eight patients (8.7%) died within 24 hours of admission, 13 (14.1%) died between 24–48 hours, and 48 (52.2%) died more than 48 hours after admission. There was no significant difference in age at arrival, birth weight, or gestational age between survivors and non-survivors. Likewise, silo dislodgment prior to final closure was not associated with an increased risk of culture-proven sepsis or in-hospital mortality (p = 0.6). At the time of arrival, 90 (97.8%) patients were treated for sepsis and started on antibiotics. Positive blood cultures were obtained in 38 (41.3%) patients. Patterns of antimicrobial use and regimens are depicted in Table 2. Blood-culture confirmed pathogens and associated outcomes are shown in Table 3.

Table 2
Patterns of antimicrobial use

Overall antibiotics use	
Received antibiotics on arrival, *n (%)*	90 (97.8)
Proportion of days on any antibiotics, mean *(SD)*	0.86 (0.20)
Received extended spectrum[a] antibiotics during stay, *n (%)*	35 (38.0)
Antibiotic regimens at admission	
Penicillin + Aminoglycoside, *n (%)*	50 (54.3)
Penicillin + Cephalosporin, *n (%)*	23 (25.0)
Penicillin + Cephalosporin + Metronidazole, *n (%)*	4 (4.4)
Penicillin + Cephalosporin + Aminoglycoside, *n (%)*	4 (4.4)
Cephalosporin, *n (%)*	3 (3.3)
Other[b], *n (%)*	6 (6.5)
None, *n (%)*	2 (2.2)
[a] Extended spectrum includes vancomycin and carbapenem	
[b] Other includes cephalosporin + metronidazole, cephalosporin + vancomycin, penicillin alone, penicillin + aminoglycoside + carbapenem, penicillin + aminoglycoside + metronidazole, penicillin + aminoglycoside + vancomycin	

Table 3
Blood-culture confirmed pathogens and associated outcomes

Pathogen	**Survived to Discharge (N = 21)**	**In-Hospital Death (N = 71)**	**p-value**
Klebsiella	5	12	0.53
Staphylococcus	7	6	< 0.01
E. coli	2	3	0.32
Acinetobacter	0	3	1.00

The most common antibiotic regimen at admission was penicillin and gentamicin (n = 50, 54.3%), followed by penicillin and cephalosporins (n = 23, 25.0%). Patients spent on average 86.2% (SD = 20.1%) of the hospital day on antimicrobial therapy. There was no difference in antimicrobial selection between survivors and non-survivors. In the subset of patients who survived to hospital discharge, the proportion of hospital stay on antimicrobial therapy was 74.2% (SD = 18.7%), which equates to an average duration

of 21 days. Thirty-five (38.0%) patients received second-line antibiotics at some point during their hospital stay. Among participants receiving second-line antibiotics, the most commonly used medications were carbapenems and vancomycin. Patients spent on average 43.2% (IQR 31%, 59%) of their hospital stay on carbapenems, 24.1% of hospital days on vancomycin (IQR 0%, 43%), and 21.4% (IQR 0%, 35%) receiving both. The shift from first-line to second-line agents occurred within the first half (35.3%, IQR 18%-48%) of a patient's hospital stay. Antibiotic susceptibilities and clinical reasoning for antibiotic escalation were not available for this retrospective cohort.

In comparing late death patients (survived ≥ 48 hours after admission) to patients who survived to hospital discharge, late death patients spent a greater proportion of hospital stay (90.0% v. 75.0%, $p < 0.001$) and post-abdominal closure stay (79.5% v. 66.9%, $p = 0.03$) on antibiotics. There was no difference in the proportion of hospital stay on extended spectrum antibiotics (16.5% v. 27.1%, $p = 0.1$).

Discussion

Frequent late deaths due to sepsis, prolonged antibiotic courses, and regular use of second-line antibiotic agents were identified in this retrospective cohort of gastroschisis patients in Rwanda. Although we did not identify a survival difference related to antimicrobial selection in this study, our findings and the team's clinical experience highlight the critical need for prospective evaluation of blood culture data and antibiotic sensitivity results to maintain an up-to-date antibiogram and control AMR in Rwanda.

In 2011, Rwanda's Ministry of Health published National Neonatal Protocols, which included empiric antibiotic guidelines for several clinical diagnoses [18]. Initial antibiotic selection in our study was in alignment with the Rwanda Neonatal Protocol, which advocates for using ampicillin and gentamicin for first-line, empiric treatment of neonatal sepsis. The duration of antibiotic therapy, however, is a major concern. Per the guidelines, a 7–14 day course of ampicillin and cephalosporin is recommended for treatment of sepsis [18]. The average duration of antimicrobial therapy among survivors in our study population was three weeks. It is important to note that survivors did spend an average of one week off antibiotics prior to hospital discharge, suggesting a satisfactory clinical response. Nevertheless, the overall duration of antimicrobial therapy was considerably longer in our cohort than recommended by the Rwandan National Neonatal Protocols. Additionally, over one-third of our study population received second-line antibiotics, such as vancomycin and meropenem, which were prescribed due to concern for AMR. The true picture of AMR, however, remains unclear due to limited antibiotic sensitivity testing.

AMR surveillance data are sparse across most of Africa, but mounting evidence points to widespread antibacterial resistance among several common culprits in surgical patients, including Staphylococcus aureus, Escherichia coli, and Klebsiella pneumonia [19]. Two systematic reviews on AMR in Africa have identified high levels of resistance to first-line antibiotics and large gaps in diagnostic capacity. In fact, AMR data is missing in 40% of African countries as of 2017 [20, 21]. Inadequate AMR surveillance presents a particularly sizeable problem for surgical neonates—a population which dies more frequently of sepsis than any other cause [7, 8]. At CHUK, blood cultures are commonplace, but antibiotic sensitivity

testing was not routinely available at the time of our study. A recent study on antimicrobial resistance patterns in Rwandan neonatal units found zero percent sensitivity to ampicillin and only 13% sensitivity to gentamicin among 128 positive blood cultures at CHUK [22]. In our study population, there was no difference in the type of pathogen identified on blood culture between survivors and non-survivors, except for reduced mortality among patients with staphylococcus-positive blood cultures, likely representing contaminated samples. It is also possible that the lack of statistical difference in blood culture results between survivors and non-survivors is due to small sample size and inadequate power to detect a meaningful difference. Nevertheless, resistance to nationally recommended empirical antibiotic regimens is a major impediment to combatting neonatal infection in Rwanda. Without reliable culture and antibiotic sensitivity data, physicians must rely on clinical suspicion for antimicrobial selection, which delays appropriate treatments, worsens antibiotic resistance to first-line antibiotics, and drives up costs for the healthcare system [10, 23]. These issues will only be amplified as neonatal critical care capacity grows in Rwanda.

At the patient level, issues with antibiotic use extend beyond AMR. Inappropriate or excessive use of antibiotics are increasingly linked to life-threatening adverse events in neonates, including late-onset sepsis, necrotizing enterocolitis (NEC), invasive candidiasis, and death [23–26]. In our study, survivors received prolonged courses of antibiotics lasting much longer than high-income setting guidelines recommend for simple gastroschisis patients (without evidence of infection) [27–29]. Prophylactic antifungal medications are also not routinely provided in our setting, as the only available antifungals are oral medications, which are not suitable for patients unable to tolerate enteral feeds. Furthermore, prolonged use of certain second-line agents may be particularly harmful in low-resource settings, where serum concentration monitoring is not feasible. Without the laboratory capacity to measure serum peaks and troughs for antibiotics like vancomycin, we are unable to monitor for nephrotoxic and ototoxic serum drug concentrations [30, 31]. Therefore, following guidelines established for high-income settings is challenging in LMICs due to differences in patient environment (open wards), resources, and AMR patterns.

Improving gastroschisis outcomes at CHUK demands much more than timely arrival to a tertiary care center, careful antibiotic management, and better AMR surveillance. Gastroschisis is a complex congenital condition which requires comprehensive neonatal care. There are multiple infrastructure, personnel, and material resource limitations to overcome in our setting [32]. At CHUK, most neonates treated for surgical diseases are outborn and unable to be admitted to the formal neonatology unit due to infection risk. This lack of centralized neonatal critical care services introduces challenges to specialized nurse training and access to neonatal-specific equipment (radiant warmers, isolettes, small gauge IVs, etc.). Since the time of our study, surgical neonates have been cohorted in a neonatal surgical unit—an evidence-based intervention that has improved surgical outcomes and resource utilization in other LMIC institutions [33, 34]. Further improvements in gastroschisis outcomes, and, more broadly, neonatal surgical outcomes, will require careful investigation to optimize multidisciplinary collaboration and daily management. This is the focus of an ongoing prospective neonatal surgical outcomes registry, through which we aim to identify modifiable risk factors for in-hospital morbidity and mortality at CHUK.

Our study has certain limitations. First, the study was conducted retrospectively and over a timeframe when neonatal surgical care was evolving at CHUK. While data is presented collectively, there were likely differences in care protocols and outcomes over this timeframe that we were unable to capture. Second, monitoring for NEC is limited to clinical exam due to unavailability of bedside x-ray and difficulty transporting unstable neonates to the radiology department. In neonates with suspected NEC, placement of percutaneous inserted central catheters (PICC lines) for total parenteral nutrition (TPN) would be the standard of care in high-income countries, but these interventions remain largely unavailable in Rwanda [29]. Finally, antibiotic selection was affected only by blood culture results; there were no urine or cerebrospinal fluid samples sent for culture. Therefore, in cases of culture-negative sepsis, antimicrobial escalation, de-escalation, and discontinuation were dependent on clinical findings alone. Antimicrobial sensitivity testing was likewise not routinely available during our study timeframe. These data will be a critical component of our ongoing neonatal surgical registry and quality improvement initiative at CHUK.

Abbreviations And Definitions

AMR: Antimicrobial resistance

CHUK: Centre Hospitalier Universitaire de Kigali

LMIC: low- and middle-income countries

Outborn: born outside of CHUK's facility

PFS: Preformed silos

Declarations

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References

1. Victora CG, Requejo JH, Barros AJD, Berman P, Bhutta Z, Boerma T, et al. Countdown to 2015: a decade of tracking progress for maternal, newborn, and child survival. Lancet 387:2049–2059. https://doi.org/10.1016/S0140-6736(15)00519-X.
2. WHO. Newborns: improving survival and well-being. https://www.who.int/news-room/fact-sheets/detail/newborns-reducing-mortality. Accessed 24 Feb 2022
3. GBD 2015 Child Mortality Collaborators. Global, regional, national, and selected subnational levels of stillbirths, neonatal, infant, and under-5 mortality, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 388:1725–1774. https://doi.org/10.1016/S0140-6736(16)31575-6.
4. UNICEF. Neonatal mortality. In: UNICEF DATA. https://data.unicef.org/topic/child-survival/neonatal-mortality/. Accessed 27 Jan 2022
5. Wright N, Abantanga F, Amoah M, Appeadu-Mensah W, Bokhary Z, Bvulani B, et al. Developing and implementing an interventional bundle to reduce mortality from gastroschisis in low-resource settings. Wellcome Open Res 4:46. https://doi.org/10.12688/wellcomeopenres.15113.1.
6. Davis JR, Nsengiyumva A, Igiraneza D, Hong P, Umutoni R, Neal D, et al. Predictors of Survival: A Retrospective Review of Gastroschisis and Intestinal Atresia in Rwanda. J Surg Res 273:138–146. https://doi.org/10.1016/j.jss.2021.12.035.
7. Ameh EA, Seyi-Olajide JO, Sholadoye TT. Neonatal surgical care: a review of the burden, progress and challenges in sub-Saharan Africa. Paediatr Int Child Health 35:243–251. https://doi.org/10.1179/2046905515Y.0000000033.
8. Ameh EA, Dogo PM, Nmadu PT. Emergency neonatal surgery in a developing country. Pediatr Surg Int 17:448–451. https://doi.org/10.1007/s003830000551.
9. Alliance for Maternal and Newborn Health Improvement (AMANHI) mortality study group. Population-based rates, timing, and causes of maternal deaths, stillbirths, and neonatal deaths in south Asia and sub-Saharan Africa: a multi-country prospective cohort study. Lancet Glob Health 6:e1297–e1308. https://doi.org/10.1016/S2214-109X(18)30385-1.
10. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet S0140-6736(21)02724–0. https://doi.org/10.1016/S0140-6736(21)02724-0.
11. Carroll M, Rangaiahagari A, Musabeyezu E, Singer D, Ogbuagu O. Five-Year Antimicrobial Susceptibility Trends Among Bacterial Isolates from a Tertiary Health-Care Facility in Kigali, Rwanda.

Am J Trop Med Hyg 95:1277–1283. https://doi.org/10.4269/ajtmh.16-0392.

12. Umutesi G, Velin L, Muwanguzi M, Faktor K, Mugabo C, Rukundo G, et al. Strengthening Antimicrobial Resistance Diagnostic Capacity in Rural Rwanda: A Feasibility Assessment. Ann Glob Health 87:78. https://doi.org/10.5334/aogh.3416.
13. Cartledge PT, Ruzibuka FS, Rutagarama F, Rutare S, Rogo T. Antibiotic prescribing practices in three neonatology units in Kigali, Rwanda. – an observational study. African Health Sciences 20:1646–54. https://doi.org/10.4314/ahs.v20i4.17.
14. Seyi-Olajide JO, Ademuyiwa AO, Alakaloko FM, Elebute OA, Bode CO. Direct observation surveillance of surgical site infections among paediatric surgical patients at a tertiary institution in Nigeria: A prospective epidemiologic study. East and Central African Journal of Surgery 24:
15. Petroze RT, Calland JF, Niyonkuru F, Groen RS, Kyamanywa P, Li Y, et al. Estimating pediatric surgical need in developing countries: a household survey in Rwanda. J Pediatr Surg 49:1092–1098. https://doi.org/10.1016/j.jpedsurg.2014.01.059.
16. Kimble RM, Singh SJ, Bourke C, Cass DT. Gastroschisis reduction under analgesia in the neonatal unit. J Pediatr Surg 36:1672–1674. https://doi.org/10.1053/jpsu.2001.27957.
17. STROBE. In: STROBE. https://www.strobe-statement.org/. Accessed 24 Feb 2022
18. Rwanda Ministry of Health. National Neonatal Protocols.
19. World Health Organization. Antimicrobial Resistance: Global Report on Surveillance. World Health Organization
20. Bernabé KJ, Langendorf C, Ford N, Ronat J-B, Murphy RA. Antimicrobial resistance in West Africa: a systematic review and meta-analysis. International Journal of Antimicrobial Agents 50:629–639. https://doi.org/10.1016/j.ijantimicag.2017.07.002.
21. Tadesse BT, Ashley EA, Ongarello S, Havumaki J, Wijegoonewardena M, González IJ, et al. Antimicrobial resistance in Africa: a systematic review. BMC Infect Dis 17:616. https://doi.org/10.1186/s12879-017-2713-1.
22. Habimana R, Rogo T. High Incidence of Bacteria Resistant to Recommended Empiric Antibiotics for Neonatal Sepsis at a Tertiary Level Neonatology Unit in Rwanda. Open Forum Infectious Diseases 2:1619. https://doi.org/10.1093/ofid/ofv133.1172.
23. Cantey J, Patel S. Antimicrobial stewardship in the NICU. Infectious disease clinics of North America. https://doi.org/10.1016/j.idc.2014.01.005. https://doi.org/10.1016/j.idc.2014.01.005.
24. Kuppala VS, Meinzen-Derr J, Morrow AL, Schibler KR. Prolonged initial empirical antibiotic treatment is associated with adverse outcomes in premature infants. J Pediatr 159:720–725. https://doi.org/10.1016/j.jpeds.2011.05.033.
25. Cotten CM, Taylor S, Stoll B, Goldberg RN, Hansen NI, Sánchez PJ, et al. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. Pediatrics 123:58–66. https://doi.org/10.1542/peds.2007-3423.

26. Lee JH, Hornik CP, Benjamin DK, Herring AH, Clark RH, Cohen-Wolkowiez M, et al. Risk factors for invasive candidiasis in infants >1500 g birth weight. Pediatr Infect Dis J 32:222–226. https://doi.org/10.1097/INF.0b013e3182769603.
27. Williams SL, Leonard M, Hall ES, Perez J, Wessel J, Kingma PS. Evaluation of Early Onset Sepsis, Complete Blood Count, and Antibiotic Use in Gastroschisis. Am J Perinatol 35:385–389. https://doi.org/10.1055/s-0037-1607420.
28. Haddock C, Al Maawali AG, Ting J, Bedford J, Afshar K, Skarsgard ED. Impact of Multidisciplinary Standardization of Care for Gastroschisis: Treatment, Outcomes, and Cost. Journal of Pediatric Surgery 53:892–897. https://doi.org/10.1016/j.jpedsurg.2018.02.013.
29. Children's Health of Orange County. Gastroschisis Clinical Guideline. https://www.choc.org/wp/wp-content/uploads/2018/06/GastroschisisClinicalGuideline.pdf. Accessed 24 Feb 2022
30. Pacifici GM, Allegaert K. Clinical pharmacokinetics of vancomycin in the neonate: a review. Clinics (Sao Paulo) 67:831–837. https://doi.org/10.6061/clinics/2012(07)21.
31. Filippone E, Kraft W, Farber J. The Nephrotoxicity of Vancomycin. Clin Pharmacol Ther 102:459–469. https://doi.org/10.1002/cpt.726.
32. Wright NJ, Sekabira J, Ade-Ajayi N. Care of infants with gastroschisis in low-resource settings. Semin Pediatr Surg 27:321–326. https://doi.org/10.1053/j.sempedsurg.2018.08.004.
33. Johnson JT, Tani LY, Puchalski MD, Bardsley TR, Byrne JLB, Minich LL, et al. Admission to a dedicated cardiac intensive care unit is associated with decreased resource use for infants with prenatally diagnosed congenital heart disease. Pediatr Cardiol 35:1370–1378. https://doi.org/10.1007/s00246-014-0939-x.
34. Khan A, Abdullah A, Ahmad H, Rizvi A, Batool S, Jenkins KJ, et al. Impact of International Quality Improvement Collaborative on Congenital Heart Surgery in Pakistan. Heart 103:1680–1686. https://doi.org/10.1136/heartjnl-2016-310533.