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ORIGINAL ARTICLE

Reduction of Microbial Contaminants in Extemporaneous Compounded Oral Medicines Following a Hand Hygiene Intervention at a Tertiary Hospital in Tanzania

Eunice G. Emmanuel[a] Caroline A. Minja[b*], Vitus Silago[c], Kayo Hamasaki[a], Martha F. Mushi[c], Stephen E. M'shana[c]

[a]School of Pharmacy, Catholic University of Health and Allied Sciences, Mwanza Tanzania; [b]Department of Biochemistry and Molecular Biology, Catholic University of Health and Allied Sciences, Mwanza Tanzania; [c]Department of Microbiology and Immunology, Catholic University of Health and Allied Sciences, Mwanza Tanzania

Correspondence to Caroline A Minja (anoldcm90@gmail.com)

ABSTRACT

Background: Extemporaneously compounded medicines are essential for individualized patient care, particularly when age-specific commercial formulations are unavailable. However, the process of compounding is susceptible to microbial contamination, which may result to product spoilage and risk to patient safety.

Objectives: This study aimed to assess the microbial quality of extemporaneously compounded oral medicines at Bugando Medical Center

Methodology: A cross-sectional study was conducted at Bugando Medical Centre (BMC) compounding unit, involving 388 freshly prepared oral compounded medicines. Samples were cultured on Blood agar, MacConkey agar, and Sabouraud's Dextrose Agar for bacterial and fungal isolation. Microorganisms were identified using colony morphology, Gram staining, and standard biochemical tests. Following initial findings, selected environmental samples and a few additional samples were collected to explore potential sources of contamination. Results were then shared with staff in the unit, who agreed to reinforce hand hygiene practices. Contamination rates were then compared before and after the hand hygiene intervention. Data was analyzed using STATA version 15 (Texas, USA).

Results: Majority of compounded medicines were diuretics 228 (58.8%), primarily prepared for children aged 1–5 years with cardiovascular conditions. Overall, 170 (43.8%) extemporaneously compounded medicine samples were contaminated. Among these, Gram-negative bacteria predominated 136 (80.0%), followed by fungi 17 (10.0%) and Gram-positive bacteria 17 (10.0%). Following reinforcement of hand hygiene practices, the overall contamination rate significantly decreased by 18.8% (P<.001).

Conclusion: A high prevalence of microbial contamination was observed for oral extemporaneously compounded medicines at BMC. Reinforcing hand hygiene and routine quality monitoring, is critical to improving the safety of compounded medicines.

BACKGROUND

Extemporaneous compounded medicines also referred to as "off-label" or "unlicensed preparations", are customized pharmaceutical products prepared from commercially available raw materials such as tablets, powders, or capsules, or through dose adjustment of licensed formulations.[1-3]
Compounding is performed in designated areas within community or hospital pharmacies to ensure the safety of such medicines. Extemporaneous compounding plays a critical role in clinical care, particularly when suitable age-specific commercial formulations are unavailable, especially for pediatric and geriatric patients.[4-6]

The demand for extemporaneous medicines is expected to increase periodically, however, limited investment in drug standardization and quality assurance may compromise their effectiveness.[4,7] In addition, instability arising from physico-chemical degradation or improper preservative use can also reduce the quality of these drugs.[8-10]

Although compounding is a core competency of pharmacists who should adhere to Good Manufacturing Practices (GMP)[11,12] routine quality control measures, including microbial testing, are often not performed for extemporaneously prepared medicines.[13,14] As a consequence, compounded medicines become more susceptible to microbial contamination from raw materials, equipment, or the environment, potentially leading to drug spoilage, treatment failure, or patient harm. Furthermore, regulatory oversight of non-sterile compounded products is limited, especially in low-income countries

which classify compounded products as "low-risk" preparations.[10,11] Such quality gaps were previously reported for *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Staphylococcus aureus* and fungi, which are associated with drug spoilage, treatment failure, and severe outcomes particularly among children and immune-compromised patients.[14-17]

In Tanzania, few healthcare facilities have established compounding units, including Bugando Medical Centre (BMC).[12] However, there is limited evidence on the microbiological quality of extemporaneous prepared medicines in such settings, routine quality surveillance is also lacking. Therefore, this study assessed the prevalence of microbial contamination in oral extemporaneous compounded medicines at BMC and reinforces the importance of adherence to hygiene practices in compounding units.

METHODS

Study Design

A hospital-based cross-sectional study was conducted between May and July 2019. Serial sampling technique was used to include freshly prepared samples of extemporaneous prepared medicines compounded at the Bugando Medical Centre (BMC) pharmacy unit during the study period until the required sample size was obtained.

Bugando Medical Centre is a tertiary referral hospital located in northwestern Tanzania, serving the Lake Zone regions. The hospital has a single compounding unit within the Department of Pharmacy and is staffed with four personnel. Approximately 25 to 40 patients with varying compounding needs are served each day, with a peak compounding load observed during the first week of each month.

Sample Size Estimation

The Kish-Leslie's formula of sample size estimation was used to calculate the minimum required sample size; $n=Z^2pq/d^2$. [18]

Where n is the required sample size, Z is the critical value (1.96), p is the estimated prevalence (50%), q = 1 − p, and d is the desired margin of error (5%). The calculated minimum sample size was 384 samples; however, a total of 388 medicine samples were collected.

Sample Collection and Transportation

Approximately 1 mL of freshly compounded oral medicines was aseptically transferred into sterile universal containers and transported to Catholic University of Health and Allied Sciences Microbiology laboratory for immediate processing.

Microbiological Testing

A volume of 3 to 5 µL from each sample was inoculated onto Blood agar (BA), MacConkey agar (MCA), and Sabouraud's dextrose agar (SDA), (Oxoid, UK). Plates were incubated at 37 °C for 24 hours (BA and MCA) and 48 to 72 hours (SDA). Microbial growth was assessed based on colony morphology, Gram staining, and standard in-house biochemical tests, fungal isolates were further identified using Candida chromogenic agar.[19]

Implementation of Reduction Measures

Following initial laboratory findings, we aimed to blindly test additional samples in the unit in order to identify potential sources of contamination. These included compounded medicine samples prepared in the unit for two consecutive days, one tap water sample and environmental swabs from the air conditioner, water sink, and compounding tabletop.

Medicine samples were collected as previously described. The tap water sample was collected in a sterile container after allowing tap water to run for two minutes while surface swabs were obtained immediately after routine morning decontamination according to specified protocol. All samples were processed and analyzed using the same microbiological procedures.

Initial findings were communicated to staff in the compounding unit, and a consensus was reached to reinforce hand hygiene practices before and during compounding. Contamination rates before and after the intervention were then compared.

Data Collection and Analysis

A pre-tested questionnaire was used to extract relevant data from compounding request forms submitted to the BMC compounding unit. Data were entered into Microsoft Excel and analyzed using STATA version 13 (Texas, USA). Categorical variables were summarized as percentages, and a $P < 0.05$ was considered statistically significant.

Quality Control

Sterility of culture media was verified by incubating uninoculated plates at 37 °C for 48–72 hours per batch; any growth led to batch discard.

Ethical Considerations

This study was ethically cleared by the joint Catholic University of Health and Allied Sciences (CUHAS) and Bugando Medical Centre (BMC) Research Ethics and Review Committee with the ethical clearance certificate number CRECU/988. Permission to conduct this study was also sought from Bugando Medical Centre's administration.

RESULTS

A total of 388 samples of extemporaneous compounded medicines were included in this study of which 228 (58.8%) were diuretics, followed by beta-blockers 34 (8.8%), antimetabolites 34 (8.8%), antimicrobials (antibacterial 16 (4.1%), antifungal (3 (0.8%) and antiviral (1 (0.3%)) and others (Table 1).

Most patients receiving medication from the BMC compounding unit were children below five (Figure 1). Considering their diagnosis, the majority, 279 (71.9%), had cardiovascular diseases followed by hematological problems 34 (8.7%) (Figure 2).

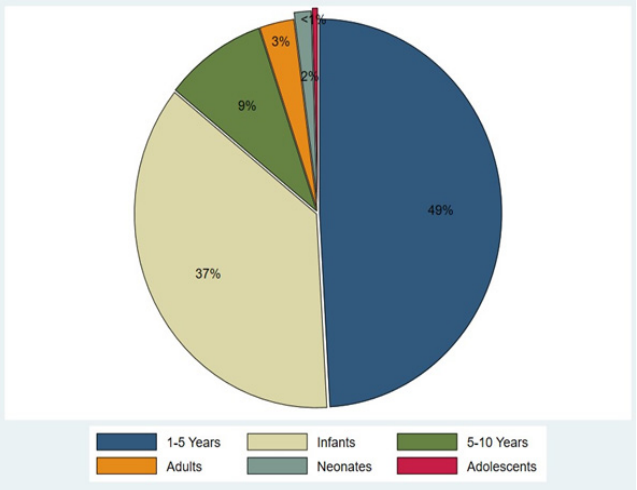
Prevalence of Contaminated Oral Compounded Medicines at Bugando Medical Centre

Out of 388 processed samples, 170 (43.8%) were contaminated, with more than half of these being diuretics 81 (55.5%), 18 (12.3%) antimetabolites, 12 (8.2%) beta blockers and others (Table 2).

TABLE 1: Pharmacological Groups of Medicines Compounded at Bugando Medical Centre

Pharmacological group	Frequency (n)	Percentage (%)
Diuretics	228	58.76
Beta-blocker	34	8.76
Antimetabolites	34	8.76
Antibacterial	16	4.12
Vasodilators	13	3.35
ACE inhibitor	12	3.09
Opioid	11	2.84
Proton Pump Inhibitors	10	2.58
Cardiac glycoside	8	2.06
Barbiturate	7	1.80
Benzodiazepine	4	1.03
Antifungal	3	0.77
Antacids	3	0.77
H1 Antagonist	1	0.26
H2 Antagonist	1	0.26
Dopamine antagonist	1	0.26
Supplements	1	0.26
Antiviral	1	0.26
TOTAL	388	100.00

FIGURE 1: Age Group of Participants Receiving Oral Compounded Medicines at BMC



The Pattern of Contamination for Oral Compounded Medicines at Bugando Medical Centre

A majority of the products, 136 (80.0%) were contaminated with Gram-negative bacteria, followed by fungi 17 (10.0%) and Gram-positive bacteria 17 (10.0%). The leading Gram-positive contaminant was *Staphylococcus epidermidis* 13 (76.5%) (Figure 3), while *Pseudomonas aeruginosa* 41 (30%), *Klebsiella pneumoniae* 38 (27%) and *Escherichia coli* 32 (23%) were the most common Gram-negative contaminants (Figure 4).

FIGURE 2: Diseases of Participants Receiving Oral Compounded Medicines at BMC

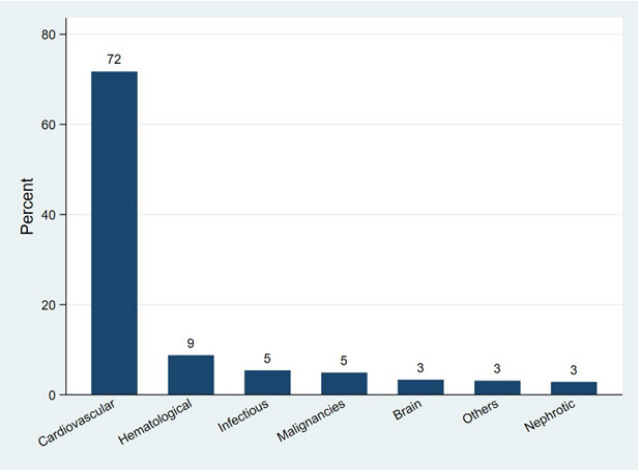


TABLE 2: Contaminated Oral Compounded Medicines by Pharmacological Groups

Drug's pharmacological group	No. of contaminated samples	Percentage (%)
Diuretics	95	55.88
Antimetabolite	21	12.35
Beta-blocker	13	7.65
ACE inhibitor	6	3.53
Antibacterial	9	5.30
Vasodilator	9	5.30
Opioids	7	4.11
Antifungal	3	1.76
Benzodiazepine	3	1.76
Cardiac glycoside	3	1.76
Proton pump inhibitors	1	0.58
TOTAL	170	100.00

Possible Source of Contamination

When tracing the possible source of product contamination *Pseudomonas aeruginosa* was isolated from tap water while Candida species was isolated from the environment (sinks and table). Nothing was isolated from products.

Impact of Hand Hygienic Implementation

Following hand hygiene practices, contamination of extemporaneous drugs was significantly reduced by 18.8% (P<.001) (Table 3).

FIGURE 3: Pattern of Gram-Positive Bacteria Isolated from Oral Compounded Medicines at BMC

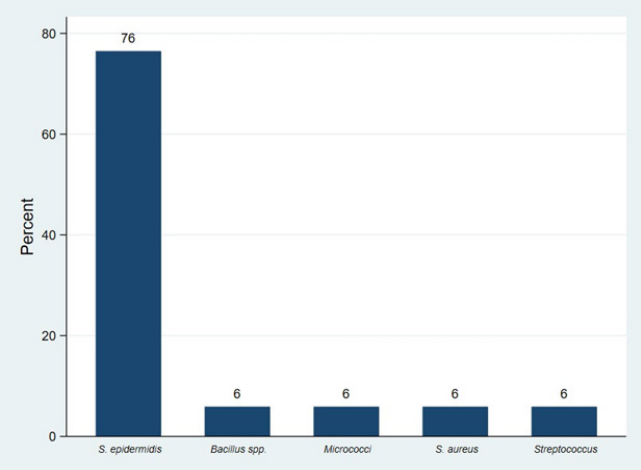


TABLE 4: Pattern of Gram-Negative Bacteria Isolated from Oral Compounded Medicines at BMC

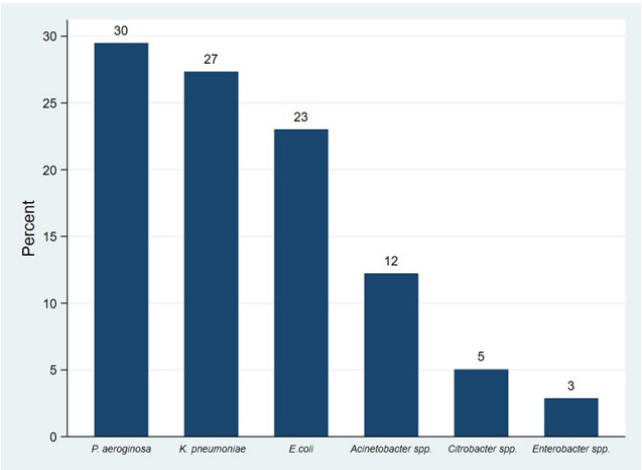


TABLE 3: Prevalence and Pattern of Contamination Before and After Hygiene Implementations

Organism	Before Implementation (n=136)	After Implementation (n=252)	Reduction rate	*P value*
Total contaminants	58(42.6%)	60(23.8%)	18.8%	<.001
Gram-negative	49(36.0%)	50(19.8%)	16.2%	<.001
Klebsiella pneumoniae	28(20.6%)	10(3.9%)	16.7%	<.001
Pseudomonas aeruginosa	21(15.4%)	20(7.9%)	7.5%	.023
Escherichia coli	20(14.7%)	12(4.8%)	9.9%	.001
Candida albicans	11(8.0%)	6(2.4%)	5.6%	.009

DISCUSSION

This study assessed the microbiological quality of extemporaneously compounded oral medicines at (BMC), identified potential sources of contamination, and evaluated the impact of improved hygiene practices.

Microbial contamination was observed in 43.8% of extemporaneously compounded medicines at BMC. This is slightly lower compared to what was observed at Amana hospital pharmacy in the same country.[20] Amana hospital pharmacy is a public outpatient pharmacy run by many personnel including staff, interns, pharmacy assistants and technicians whose handling of medicines risks higher contamination rates compared to BMC, a private hospital with the compounding unit confined to few personnel.

Majority of compounded medicines at BMC were diuretics (58.8%) primarily prepared for children aged 1 to 5 years with cardiovascular conditions. This is slightly higher compared to what was reported in Pakistan where 26.1% of unlicensed drugs were extemporaneous preparations,[21] but lower than what is expected for developing countries like Tanzania.[22] The increasing burden of non-communicable diseases among pediatrics and the lack of commercially available age-appropriate formulations explains increased rate of compounding for pediatric patients in this study and elsewhere. [6,22]

We also observed a high prevalence of compounded medicines contaminated with Gram-negative bacteria pathogens (80.0%). This is comparatively high compared to what is expected from primary healthcare compounding centers where non-experienced healthcare workers are involved with compounding. [16] Specifically, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Escherichia coli* were isolated at comparable frequencies (Figure 4). This corroborates with data reported in Dar-es-salaam and other parts of Africa[22-24] for Gram-negative predominance in compounded medicines. Despite the unit's location in

a referral hospital where good manufacturing practices are anticipated, a high prevalence of microbial contaminants is reported for compounded medicines in this study. A possible non-adherence to good manufacturing practices or standard preparation procedures exists at the BMC compounding unit as supported by reduced contamination rates observed after hand hygiene enforcement in the unit. Likewise, Gram-negative bacteria are not expected in final compounded products but could be from raw materials, environment/surfaces or water sources in compounding units. This was also observed in this study as Gram-negative bacteria and fungi persisted after hand hygiene enforcement but were not isolated from medicinal products. As a consequence, the persistence of Gram-negative organisms ensures that tap water and compounding environments are reservoirs of microbial contaminants that can render product unsafe, as observed in this study.

Gram-positive contaminants including *Staphylococcus aureus*, *Bacillus species*. *Micrococci species* and *Streptococci* species were isolated at comparable frequencies to that previously reported for compounded medicines,[22] but *Staphylococcus epidermidis* was the most predominant isolate in this study. Previously, *S. epidermidis* was also isolated from compounded products,[24] equipment and raw materials used in the process. [24,25] As a normal flora and opportunistic pathogen, *S. epidermidis* is a challenge to product safety and was possibly introduced in these products by staff working in the unit through poor hand hygiene and inadequate aseptic techniques during compounding. Proper personnel and environment hygiene during compounding can prevent product contamination and improve product quality as observed in this study.

Following hand hygienic improvements, we observed a significant reduction and total elimination of microbial contaminants in the final products (Table 3). Only Gram-negative and *Candida* species persisted. The findings are similar to that from a previous study where *Candida spp*. and *Acinetobacter spp*. were reported from air conditioners and surfaces of compounding environments and could persist up to 4 months.[22] *Pseudomonas aeruginosa* is frequently isolated from tap water due to its ability to form biofilms and survive in water systems[2, 26] emphasizing the need for routine disinfection and environmental monitoring in compounding units. Gram-positive bacteria are sensitive to disinfectants and antiseptics and may be the reason for their complete elimination. This parallel underscores that while hand hygiene is highly effective against Gram-positive contaminants, persistent Gram-negative and fungal contaminants likely stem as reservoirs of contamination in compounding units.

Study Strength and Limitations

This study was a single centered cross-sectional study that limits a causal-effect inference, however the sub-analysis conducted suggests the possible source of contamination and the impact of our intervention. Future longitudinal studies are encouraged to better ascertain the root-cause of contamination in these products.

CONCLUSION AND RECOMMENDATION

A substantial proportion of extemporaneously compounded medicines at Bugando Medical Centre were contaminated with microorganisms, posing potential risks to patient safety. Reinforcement of hand hygiene significantly reduced contamination rate, and in order to reduce microbial load in the final product, sustained personnel and environmental hygiene must be monitored in the unit.

Based on these findings, we recommend the establishment of regular personnel, environment and equipment sanitation protocol at the BMC compounding unit. Further research should explore other hygiene interventions and their long-term sustainability to ensure the quality of these medicines. Moreover, additional sources of contamination, such as excipients or packaging materials should be traced to prioritize resources allocation for complete mitigation of product contamination.

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