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Drug Use Evaluation of Crystalline Penicillin in Pediatrics Ward of Dessie Referral Hospital, North East Ethiopia: A Hospital Based Cross Sectional Study

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ABSTRACT

Background: Antibiotic resistance is a worldwide issue due to rise of antibiotic consumption and wide variation in antibiotic prescribing practices. Crystalline penicillin is the most highly consumed antibiotics by hospitalized pediatrics patients in Dessie Referral Hospital and its utilization pattern is not known in the study area. The objective is to assess the appropriateness of crystalline penicillin use in pediatrics ward of Dessie Referral Hospital, Northeast Ethiopia.

Methods: A hospital based cross-sectional study was used for evaluating medication records of hospitalized pediatric patients who received crystalline penicillin from October to December 2018.

Results: A total of 262 hospitalized pediatrics patient records were included in the study. All the 262 (100%) cases were consistent with guidelines for contraindication and drug interaction to use the drug. Crystalline penicillin use was consistent with guideline recommendations in 93.8%, 92.8%, 89.6%, 66.7% and 39.4% of the cases with regard to, indication, outcome, frequency, dose and duration of treatment, respectively. The observed value of all drug utilization evaluation parameters except drug interaction and contraindication showed statistically significant difference from the set threshold in nonparametric binomial test.

Conclusion: The result of the current study especially with regard to dose and duration is much below the recommended threshold and needs scheduled trainings and necessary interventions to tackle the problem.

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Introduction

Drug use evaluation (DUE) is a system of ongoing, systematic criteria-based evaluation of drug use that will help ensure that medicines are used properly at the individual patient level (1). It is a comprehensive review of patients' prescription and cards before, during and after dispensing in order to assure right therapeutic decision making and positive outcome (2). A DUE can be structured to assess the real process of prescribing, dispensing or administering a drug and it covers indications, dose, frequency, duration of treatment (3).

Antimicrobials are used to decrease morbidity and mortality from infectious diseases, but the control of infectious diseases is threatened by the stable increase in the number of microorganisms that are resistant to antimicrobial agents (4). Antibiotic resistance is a worldwide issue due to rise of antibiotic consumption and wide variation in antibiotic prescribing practices. The most common causes of irrational drug use are inappropriate use of antimicrobials, overuse of injections when oral formulations are more appropriate, the use of too many medications per prescription, failure to adhere to guidelines while prescribing medications, inappropriate self-medication (3, 5).

Overuse of antibiotics can result in development of newly resistant bacteria strains, raising costs of health

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services, prolonged hospitalization, development of side effects and deaths (6). The adverse effect of misuse of antibiotics is more serious in children than adults (7). In developing countries, it is evident that antibiotics are prescribed for 44 to 97% of hospitalized patients often unnecessarily (8). Empirical use of antibiotics is a common practice in developing countries including Dessie Referral Hospital (DRH) and there is no STG for referral hospitals. This can result in serious resistance problems unless it is studied periodically. Crystalline penicillin is the most commonly used antibiotics in DRH of hospitalized pediatric patients. Antibiotic with a risk of abuse, high consumption rate, and that was not being controlled by antibiotic prescribing restriction system were the criteria used for selection of crystalline penicillin in the present study. To our knowledge, there is no adequate studies address crystalline penicillin use evaluation in Ethiopia and there is no previous study in DRH. Therefore, conducting the present study is logical to assess crystalline penicillin use and its appropriateness in accordance with World Health Organization (WHO) DUE guideline (3), and WHO guideline for management of common illness in pediatric patients in areas of limited resources (9). The finding of this study provides information on status of crystalline penicillin use which further helps to take appropriate measure on that specific problem to prevent misuse of crystalline penicillin.

Methods

The study was conducted from January to March 2019 in hospitalized pediatric patients admitted from October to December 2018 in DRH. The hospital is located in Dessie Town, Northeast Ethiopia, 401 km northeast of the capital city, Addis Ababa. Dessie Referral Hospital is the only referral hospital in this part of the country, with catchment population of seven million. The hospital has 200 beds and 165 healthcare professionals. The pediatric wards have 52 beds and 12 health professionals (2 general practitioners, 1 pediatrician and 9 nurses).

Ethical approval was obtained before the starting of the study from the ethical review committee of college of medicine and health sciences, Wollo University. The management of the hospital was requested for cooperation with a formal letter from Wollo University. During and after the data collection process all patient-related data were kept confidential.

A hospital based retrospective cross sectional study was used to evaluate utilization pattern of crystalline penicillin in pediatric ward of DRH in the study period.

According to the Joint Commission on Accreditation of Healthcare Organizations (JCAHCO) criteria which mandates: if the average number of cases per quarter is more than 600, at least 5% cases are reviewed; if the number of cases per quarter is fewer than 600, at least 30 cases are reviewed and if there are fewer than 30 cases per quarter, then 100% of the cases are reviewed (10). Based on these criteria, patient medication records containing crystalline penicillin and targeting pediatric patients was considered retrospectively for a quarter (October to December 2018).

From the study which encompassed data of three-month crystalline penicillin use in pediatric ward, the number of cases per quarter with crystalline penicillin indication was found to be 524. Therefore, to obtain greater point estimate of population, about 262(50%) medication records were taken as the final sample size which is much greater than the minimum sample size (n=30) as per JCAHCO recommendation.

After the sample size had been determined for the study, systematic random sampling was employed to obtain sample population. Sampling frame was prepared by coding 524 medication records according to date of records and sampling interval was calculated as follows:

K= Study population/ calculated sample size = 524/262 = 2

Once the first sample was randomly selected, all the rest samples were taken by picking every 2nd of the medical record until the required sample was obtained.

Independent variables including: Patient characteristics: age, sex, weight and diagnosis. And dependent variables including: Indication, Dose, Frequency, Duration of treatment, Contraindication, Drug interaction.

Patients' medication records were used to collect data. Data collection format was developed based on WHO recommendation (3). Pretest was done on 10% of medical records (27 medical records) to check the validity and reliability of data collection format. The pretest sample size is within the range of different literature recommendations (11). The data were collected by 2 senior clinical pharmacists. Drug use evaluation criteria with thresholds was set based on the WHO guide for DUE and WHO Guidelines for the management of common illnesses in children in areas where limited resources are considered (3,9) or (see Table 1).

The primary outcome measures were appropriateness of crystalline penicillin use with regard to the six DUE parameters and the secondary outcome measures were death, clinical improvement and switch to oral therapy. Finally, the collected data was analyzed using SPSS version 20. The non-parametric binomial test was used to analyze the data and the p value of < 0.05 was considered statistically significant.

The inclusion criteria for this study was all hospitalized pediatric patients receiving crystalline penicillin in DRH from October to December, 2018. Incomplete medical records and medical records with underlying renal and hepatic disease were excluded from the study.

Table 1. Drug use evaluation criteria for crystalline penicillin.

Indicator	Criteria	Threshold
Indication	Severe Pneumonia Pyogenic meningitis (Meningococcal meningitis and Pneumococcal meningitis) Generalized Neonatal tetanus Congenital syphilis Neonatal sepsis Cellulites Erysipelas Endocarditis	100
Dose & frequency	Bacteremia: 25,000 to 50,000 units/kg/dose IV infusion over 30 minutes, or IM Severe Pneumonia: 50,000 units/kg/24 hours IV QID Meningococcal meningitis: 250,000 units/kg/dose IV infusion over 30 minutes, or IM every 4 hour Pneumococcal meningitis: 250,000 units/kg/dose IV infusion over 30 minutes, or IM every 4 hour Neonatal sepsis: 50,000 IU/kg/24hours IV QID Neonatal tetanus: 50,000 IU/kg/24hours IV QID Cellulites: 50,000 IU/kg/24hours IV 4 hourly Erysipelas: 50,000 IU/kg/24hours IV Prevention of Bacterial Endocarditis: 50,000 IU/kg intravenously or intramuscularly 30 to 60 minutes before the procedure and, 1 million IU (25,000 IU/kg for children) six hours later Gonococcus infection (only with proven penicillin-susceptible isolate): 100,000 units/kg/dose IV infusion over 30 minutes, or IM Congenital syphilis: 50,000 units/kg/dose IV over 30 minutes, given Q 12 hours during the first 7 days of life	95
Duration	Congenital syphilis: 10-14 days Severe Pneumonia: 3 days Meningococcal meningitis: 10 days Pneumococcal meningitis: 7 days Neonatal sepsis: 10 days Neonatal tetanus: 10 days Cellulites: 10 days Erysipelas: until the fever subside Endocarditis: 2-6 weeks	90
Contraindications	Penicillin hypersensitivity reaction, avoid intrathecal route	100
Drug interactions	• Methotrexate, • Probenecid (decrease renal tubular secretion of penicillin's) • Aminoglycoside (inactivated by high dose of benzyl penicillin; should not be administered in the same giving set	90
Outcome	• Fever reduction ✓ Decrease of at least 1°c from peak temperature within 3 days of initial crystalline penicillin • Clinical characteristics noted in progress ✓ New organism or another infection suspected or identified ✓ Patient discharged before therapy completed and unavailable for follow up ✓ Patient expired • Switch to oral therapy	95

Results

A total of 262 cases were included in the analysis. From patient records, the majority of patients were found to be males 160 (61.1%) and the majority of age group falls in the 1-12 months (43.1%) (Table 2). Among the diseases for which crystalline penicillin was prescribed, severe pneumonia and sepsis were the most common indication constituting 114 cases (43.5%) and 82 cases (31.3%), respectively (Table 3). In the present study, the lower percent of appropriateness of crystalline penicillin use was found in dose 164 (66.7%) and duration of therapy 97 (39.4%) (Table 4).

Table 2. Age and sex distribution in pediatrics wards of DRH.

Age in month	Male		Female		Total	
	No	%	No	%	No	%
Less than 1	56	21.4	41	15.6	97	37
1-12	79	27.1	42	16	121	43.1
13-60	11	4.2	10	3.8	21	8
61-120	9	3.4	5	1.9	14	5.3
121-192	5	1.9	4	1.5	9	3.4
Total	160		102		262	100

Table 3. Disease state and assessment of indication of crystalline penicillin.

	Assessment	No of patient	%
Correct indication (n=246)	Severe pneumonia	114	43.5
	Sepsis	82	31.3
	Pyogenic meningitis	28	10.7
	Tetanus	12	4.6
	Cellulitis	10	3.8
Incorrect indication (n=16)	Acute gastroenteritis	6	2.3
	Neonatal asphyxia	2	0.8
	Birth injury	2	0.8
	Preterm	6	2.3

Table 4. Assessment of crystalline penicillin use with regard to dose, duration and frequency.

Indicator	Criteria	No	%	Total
Dose	Correct	164	66.7	246
	Low	42	17.1	
	High	40	16.3	
Duration	Correct	97	39.4	246
	Short	120	48.8	
	Long	29	11.8	
Frequency	Correct	220	89.4	246
	Incorrect	26	10.6	

Clinical improvement was seen in 243 (92.8%) hospitalized pediatric patients, which were identified from conversion to oral therapy and discharge summary, but nineteen patients were expired while receiving crystalline penicillin and gentamicin. The observed value of all DUE parameters except drug interaction and contraindication showed statistically significant difference from the set threshold in nonparametric binomial test.

Crystalline penicillin was most commonly converted to amoxicillin syrup 91 (78.4%) and cotrimoxazole 16 (13.8%), respectively (Table 5). Generally, there were 280 drugs co-administered with crystalline penicillin. The most common co-administered drugs were gentamycin 116 (28.6%), paracetamol 74 (18.2%), chloramphenicol 28 (6.9%), diazepam 12 (3%) and phenytoin 12(3%).

Table 5. The pattern of conversion of crystalline penicillin to other drugs.

Crystalline penicillin converted to	No. of patients	Percent
Cotrimoxazole syrup	16	13.8
Amoxicillin syrup	91	78.4
Chloramphenicol capsule	2	1.7
Augmentin capsule	5	4.3
Total	114	100

In the overall evaluation of crystalline penicillin use, hopeful results were obtained in cases of frequency of administration. However, great deviation was observed in cases of indication, dose and duration of crystalline penicillin therapy when the observed values were compared to the threshold value (Table 6).

Table 6. Summary of actual performance versus set criteria and thresholds for crystalline penicillin use.

Criteria	Threshold No. (%)	Actual performance No. (%)	P-value
Indication	262 (100)	246 (93.9)	< 0.001
Dose	249 (95)	164 (66.7)	< 0.001
Frequency	236 (90)	220 (89.6)	< 0.001
Duration	249 (95)	97 (39.4)	< 0.001
Contraindication	262 (100)	262 (100)	0.853
Drug interaction	236 (90)	262 (100)	0.625
Outcome	249 (95)	243 (92.8%)	0.04

Discussion

The main objective of DUE is to confirm that drugs are used in safe, economically viable, cost-effective approach in order to improve the therapeutic outcome of patients. Moreover, DUE aids to bring progressive improvement in the utilization

pattern of drugs and this in turn can lower the healthcare cost to the individual patient and to the facility, reducing adverse drug reactions and drug interaction, improving patient adherence and maximizing therapeutic outcomes (3,12). The knowledge of the physicians to diagnose the disease, select the right drugs, dose, dosage form and routes of administration, and without probable or suspected adverse reactions, drug interactions, and unnecessary duplication of therapy is crucial for the success of therapy. Rational drug use can be promoted by developing and applying hospital based drug formulary and STGs. Prescribers should prescribe drugs according to STGs (3, 9).

In the present study, 262 medication records which contain crystalline penicillin were taken from pediatrics wards.

Concerning with indication of crystalline penicillin, the study revealed that 246 (93.9%) of the indications were appropriate as per the STGs and this was found less performance as compared with the threshold set for indication of crystalline penicillin (100%) (3, 4). The result of this study was lower than the result of the study done in Jimma University Specialized Hospital (JUSH) in which the use of crystalline penicillin met 100% the recommendation threshold (13). In contrast, this finding was higher than the finding in Hiwot Fana Specialized University Hospital (HFSUH) where 81.58% of crystalline penicillin indications were found to be appropriate (14). In this study, severe pneumonia was the most common indication for crystalline penicillin use 114 (43.5%), followed by sepsis 82 (31.29%). Similar results were reported from study done in Nepal where among all patients prescribed with antibiotics, pneumonia was the most common diagnosis (15). In the present study, there were 6.1% of the cases for which crystalline penicillin was indicated beyond the recommendation of the guideline (9). The reason for this inappropriate use may be due to lack of documenting each diagnosis clearly, shortage of drug information and inadequate experience of prescribers.

Concerning to the dose of crystalline penicillin, different doses are employed for varieties of infections and its dose also varies in different age groups. Low dose of the drug results in emergence of antimicrobial resistance and reduces effective therapeutic outcomes whereas, over dose results in toxicological concerns. Thus, for better therapeutic outcomes, optimal dose has to be used (5, 16). In the current study, about 66.7, 17.1 and 16.3% of medical records had correct doses, under doses and overdoses of crystalline penicillin, respectively. In this study, the use of crystalline penicillin with regard to dose and frequency was found to be appropriate as per WHO DUE guideline only in 66.7% and 89.6% of crystalline penicillin containing medical record. These results were found to be below the threshold set (95%) (3). These results are lower than the results of the study in Jimma University Specialized Hospital and Hiwot Fana Specialized University Hospital (13, 14).

Resistance has become a great problem associated with premature discontinuation of therapy or shorter drug regimen than expected for the particular clinical condition. On the other hand, prolonged use of crystalline penicillin can also lead to emergence of antimicrobial drug resistance. Moreover, long duration therapy may also cause normal flora to be affected and hence foreign infections easily develop resistance. Therefore, it should be used properly as per STGs. The major problem revealed by this study was inappropriate duration of therapy. About 48.8 and 11.8% of cards had short and long duration of therapy, respectively. Only 39.4% cards contain crystalline penicillin prescribed with appropriate duration of therapy, which is very far from the threshold set by the guideline (90%) (3).

Studies in Jimma University Specialized Hospital and Hiwot Fana Specialized University Hospital revealed 83.6 and 51.75% of duration of treatments were as per STGs recommendation, respectively. These results are higher than the current study (13, 14). The discrepancy might be due to difference in experience of prescribers and drug information services.

In case of drug-drug interaction, concurrent uses of two or more drugs are recommended in defined situations based on pharmacologically rational use of drugs. However, selection of appropriate combinations requires an understanding of the potential for interaction between drugs in order to avoid the negative impact of drugs to the patient. In the present study there were no observed or documented drug-drug interactions and the result is in line with the threshold set for crystalline penicillin (90%) (3). The result of this study is similar with other studies (13, 14).

Concerning contraindication, history of hypersensitivity reaction to crystalline penicillin and other drugs were not observed or documented. The result is in line with the threshold set for contraindication for crystalline penicillin use which requires 100% free from contraindication. This result of the current study is similar with other studies done in Ethiopia (13, 14).

From a clinical perspective, the conversion of intravenous route to oral route can be done earlier in treatment if clinical improvements are observed (including increase in the level of activity, improvement in appetite, and decreased fever for at least 12-24 h and stable mental status) there by decrease infusion related adverse events, cost for intravenous (IV) lines, and development of secondary hospital acquired infection. The proper conversion of IV to oral therapy was found to result in clinical efficacy, fewer complications, shorter hospital stays, and cost savings (17).

In the present study, crystalline penicillin was converted to oral amoxicillin in 78.4% of medical records containing severe pneumonia diagnosis which met the WHO guideline for management of common illness in children in areas

with limited resources (9). However, the rest of crystalline penicillin was converted to cotrimoxazole syrup (13.8%), Augmentin (4.3%) and chloramphenicol (1.7%) which are not according to the WHO guideline for management of common illness in children in areas with limited resources. The pattern of conversion of crystalline penicillin to oral therapy in the current study was different from the study done in Jimma University Specialized Hospital. The reason for this difference might be due to difference in prescribers' experience (13).

In the present study, clinical improvement was seen in 243 (92.8%) hospitalized pediatric patients though it is below the set threshold. With regard to clinical improvement, the present study is in line with the study done in Jimma University Specialized Hospital but higher than the result of the study done in Hiwot Fana Specialized University Hospital (13, 14). The limitation of the present study was the incomplete patient records as all necessary patient information were not documented. This brings difficulty to determine appropriateness of crystalline penicillin use.

In conclusion, Crystalline penicillin use pattern in pediatric ward of DRH has not fully adhered to WHO Guideline for all used indicators in the present study. Especially, the use of crystalline penicillin with regard to dose and duration of therapy is very far below from their respective thresholds set in the DUE criteria. Result of the study showed that inappropriate use of crystalline penicillin is high which needs urgent measure to prevent the emergence of bacterial strains that are resistant to the available antimicrobial agents.

Inappropriate use of crystalline penicillin is higher in the present study. Our recommendation includes the following: Prescribers should follow the national standard treatment guideline, the hospital should strengthen scheduled trainings and the government should encourage the role of clinical pharmacists in the study area to tackle the problem.

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