Drug Related Problems and Complications of Bacterial Meningitis Admitted to Pediatrics Ward in Developing Country

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Research

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Abstract

Background: Bacterial meningitis is considered a medical emergency and it is a life-threatening infection that requires immediate treatment. However, even with an early diagnostic approach and adequate treatment with effective antibiotics, death and different complications may occur.

Objective: This study aimed to assess drug related problems and its association on bacterial meningitis related complication.

Method: A prospective hospital-based observational study was conducted at the pediatric ward of Hiwot Fana Specialized teaching hospital, Harar. This study was conducted longitudinally for consecutive one year from December 30/2019-Juanuary 1/2021 admitted to pediatrics ward. All pediatrics admitted with the diagnosis of bacterial meningitis and fulfilled the inclusion criteria. To identify independent predictors of bacterial meningitis related complication, binary logistic regression model were used using STATA, version 14.2. Stastical significance was declared at $p < 0.05$

Result: After 1 year follow up, 384 children were included in this study with a response rate of 98.1%. Males(55.73%) outnumbered. The mean age and cerebrospinal fluid protein were 5.01 ± 0.19 and 60.5 ± 4.53 respectively. Nearly half of the child had co-morbidity in addition to admission diagnosis, meningitis. Two hundred twenty four(58.33%) patients exposed to at least one type of drug related problem. One hundred twenty one (31.51%) children were developed bacterial meningitis related complications. Drug related problem(AOR=6.26, 95%CI: 3.58-10.93), cerebrospinal fluid protein(AOR=9.38, 95%CI: 9.81-9-96), age(AOR=0.01, 95%CI: 0.13-0.19), duration of illness(AOR=) and co-morbidity(AOR=13.18, 95%CI: 1.81-5.6) were absolutely associated with the occurrence of complication.

Conclusion: Drug related problem and associated complications were substantial among children admitted with meningitis. This study identified significant association between drug related problem and complication. Health professional shall prevent drug related problem to prevent associated complication.

Introduction

Bacterial meningitis (BM) is considered a medical emergency, because it is a life-threatening infection that requires immediate and appropriate treatment. Therefore, early identification of pathogens and antibiotics therapy initiation is crucial to improve treatment outcome of BM in children (1). However, even with an early diagnostic approach and adequate treatment with effective antibiotics, death and different complications may occur as bad outcomes of this infection (2). These complications might happen especially if the patients are treating inappropriately (if medications are used irrationally). The previous report showed that 57(63.33%) of children developed one or more types of complications including mental retardation, secondary epilepsy, hydrocephalus, hearing impairment and movement disorders (3).

Many patients do not receive the intended beneficial effects of their treatment as a resulted from drug related problems (DRPs). When DRPs are not identified and/or resolved, patients may experience treatment failure, adverse drug events, suboptimum quality of life, health care cost increment, facing new medical conditions and mortality(4, 5). In addition, problems involving medication are associated with emergency department visits,

prolonged hospitalizations, frequent visits to the physician's office, and additional prescriptions with increment of health care cost in both patient and health facility perspective(6).

DRPs might lead to unnecessary medication related burden and even mortality. The previous study showed that the overall, medication-related morbidity accounts for 7.0% of hospitalizations and has led to unnecessary health care expenditures in billions of dollars (7).

These populations are highly susceptible to develop DRPs affected with it because of different clinical heterogeneity (i.e. rapid body growth/ weight change, gestational age, postnatal age, and physiologically immature) and in association with it, difficulty of clinical practice patterns such as dose calculation as a function of body weight and body surface area(8–10).

The previous study investigated the magnitude and types of complications and DRPs. However, these studies were not touch the association of DRPs and complications. This study is amid to evaluate the impact of DRPs on the occurrence of bacterial meningitis related complications among children admitted with meningitis.

Method And Participants

Study area and period

This study was a prospective hospital-based study, conducted at the pediatric ward of Hiwot Fana Specialized teaching hospital(HFSTH), Harar. This study was conducted longitudinally for consecutive one year from December 30/2019-Juanuary 1/2021 admitted to pediatrics ward and stayed for more than 24 hours.

Study design

Hospital based prospective observational study was used to assess DRPs and complications among children (up to 18 years old) admitted to pediatrics ward.

Case identification

BM was defined according to clinical findings including fever, headache, altered mental status, meningeal irritation signs (Kernig or Brudzinski signs or neck stiffness), bulging fontanel $\geq$ 1 year) and elevated CSF protein ($>100\text{mg/dl}$), low CSF glucose ($< 40 \text{ mg/dl}$) or leukocytosis ($> 100 \text{ WBC/mm}^3$) with at least 80% neutrophill(11). Complication is defined as if the patient developed new cases including hydrocephalus and seizure after meningitis is confirmed.

Inclusion criteria: All children with age 1 month to 18 years, children whose hospital stay is more than 24 hours, patients admitted to pediatric ward from December 30/2019-January1/2021and caregivers are willing to participate were considered as the study population. Finally, all children who satisfy the inclusion criteria were candidate as a subject for the study.

Exclusion criteria: Re-hospitalized during study period, patients/care givers self-discharged before 7 days of treatment and whose diagnosis is changed to non-bacterial meningitis or other diagnosis before discharge.

Study variables

As usual, in this study we included both dependent and different independent variables (variables that can affect the occurrence of complication). The incidence of BM complication was dependent variables where as length of hospital stay, age, sex, co-morbidity, number of drugs, time of antibiotics initiation, different laboratory investigation, initiation of corticosteroids and presence of DRPs.

Sample size determination

Because this is a prospective observational study conducted for one year, a time bounded sample size was used. That means all children admitted to the hospital, fulfill all inclusion criteria and admitted within the data collection period were included as a study participant.

Data collection procedures

All patients were examined daily for BM related complications and DRPs. BM related complications such as seizures, persistent altered state of sensorial, hydrocephalus, comma, hearing impairment, cranial nerve palsy or any neurological deficit were checked during daily examination. CT scan of brain was done in patients having neurological deficit to detect acute complications of meningitis like, subdural effusion, hydrocephalus or brain abscess. The identified DRPs were classified according to Cipolle's method (12) as unnecessary drug therapy, needs additional drug therapy, ineffective drug therapy, dose too low, dosage too high and adverse drug reaction was recorded using structured questionnaire. For the aim of this study, both DRPs and complications were dichotomized as (children had DRPs and who are free from DRPs) and (children who developed one or more complications and who were free from it) respectively.

Data quality assurance

We have tried a lot to keep the quality of data processing starting from data collection to analysis so as to draw conclusive information. Pre-test was conducted on 5% of study participants before the actual data extraction. This pre-test is essential to check the language barrier, if variables might be missed, readability problem, and the data collector might misunderstood essence of the question. However, there was no amendment of data collection tool. Two pharmacists were involved for data collection. For this research we recruited one physician for supervision. Two days training was given for data collectors and a supervisor. The focus of training was on how to approach patient, decision of DRPs and meningitis complications in collaboration with other senior staffs, data collectors were extracted data from patient chart and laboratory requests. There was continual communication between the principal investigator and the data collector and supervisor and facilitate discussion time if concerns raised. If information in the patient chart was confusing, clarification was made by respective physician and nurse and if necessary the caregiver or the patient. We used Naranjo scale and Micro-medex version 3.1 for suspected adverse drug reaction and drug-drug interaction respectively.

Data analysis

Data analysis was computed using STATA version 14.2(Texas, USA). Before analysis, independent variable interaction, co linearity and binary logistic regression model fitness were checked. Chi-square statistics were used to check adequacy of cells for binary logistic regression analysis. Mean and median was used for continues variables whereas percentage and frequency were reported for categorical variables respectively. Univariate model was computed to identify variables which are candidate for multivariate model. Variables with $p < 0.25$ were included in the multivariate binary logistic regression model. Finally, a multiple binary logistic regression model was computed to identify determinant predictors of complication and those variables with $P < 0.05$ was declared as significant predictors.

Results

Participant demographic and clinical characteristics

A total of 384 children with meningitis were included in the current study with response rate of 98.1%. Of this 368(95.83%) were acquired from the community. Males 214 (55.73%) outnumbered the females 170 (44.27%). The mean age was 5.01 ± 0.19 . The mean gestational age of the participant was 36.38 ± 2.48 . The mean duration of illness and length of hospital stay were 2.62 ± 1.07 and 10.12 ± 3.45 respectively. One hundred eighty six (48.44%) participants had at least one co-morbidity on top of admission diagnosis with sever acquired community pneumonia was the top ranking co-morbidity. Of the approached participants 136(35.42%) were fully vaccinated and 35(9.11%) were unknown their vaccination status. Both culture and susceptibility test were not done in all of the participants. Patient demographic and clinical characteristics are shown in the (Table 1).

Table 1
Demographic, laboratory and clinical characteristics of pediatrics patients, pediatric ward of HFSTH, Harar, Ethiopia

Variables	Category	Number	Percent	Mean + SD	Range
Sex	Male	214	55.73		
	Female	170	44.27		
Age				5.01±0.19	1-16
Gestational age				36.38±2.48	35.6-42.4
Co-morbidity	Yes	186	48.44		
	No	198	51.56		
Immunization status	Fully immunized	136	35.42		
	Partially immunized	65	16.93		
		148	38.45		
	Not immunized	35	9.11		
	Not known				
Types of meningitis	Community acquired	368	95.83		
	Hospital acquired	16	4.17		
Complications	Yes	121	31.51		
	No	263	68.49		
Duration of illness before antibiotics/days				2.62±1.07	1-6
Duration of fever before antibiotics initiation /days				2.3±0.94	1-7
Temperature at admission				38.6±0.51	35.5-38.9
LP done before antibiotics initiation	Yes	320	83.33		
	No	64	16.67		
Neutrophill count				68.06±15.8	
CSF protein(mg/dl)				60.5±4.53	
CSF glucose(mg/dl)				45.72±11.34	20-86
Culture	Yes	0	0		
	No	384	100		

Variables	Category	Number	Percent	Mean + SD	Range
Susceptibility test	Yes	0	0		
	No	384	100		
Length of hospital stay/days				10.12±3.45	7-22
LP: lumbar puncture; CSF: Cerebrospinal Fluid; SD: standard deviation					

Drug Related Information

Four hundred forty five prescriptions were prescribed with a total of 730 medications. The average number of drugs per patient was 2.25. Initially, ceftriaxone + Vancomycin (50.52%) were the most frequently prescribed followed by ceftriaxone alone (29.95%). All of the admitted patients took at least one non antibiotic medication and 327 patients had been on steroid (Table 2).

Table 2
medications prescribed for children admitted to the hospital, HFSTH, Harar, Ethiopia

Variables		Frequency	%
Initial antibiotics regimen	Ceftriaxone + Vancomycin	194	50.52
	Ceftriaxone	115	29.95
	Ceftriaxone + Ampicillin	46	11.98
	Gentamycin + Ampicillin	29	7.55
Regimen changed	Yes	60	15.62
	No	324	84.38
Regimen changed to	Ceftriaxone + Vancomycin	45	75.00
	Vancomycin added	3	5.00
	Ceftriaxone added	12	20.00
Non antibiotics	Phenobarbital + Paracetamol	30	7.81
	Paracetamol + steroid	113	29.43
	Phenytoin + Phenobarbital +steroid	98	25.52
	Iron	16	4.16
	Vit K + steroid	116	30.21
	Phenobarbital + Vitamin K	11	2.87

Two hundred twenty four (58.3%: 53.4-63) patients had one or more than one of DRPs with the average number of DRPs/patient was 1.92. Unnecessary drug is the most common type of DRPs (30.8%) followed by need additional drug (23.66%), ineffective drug (17.4%), dose to low (14.73%) (Table 3). Antibiotics and antipyretics were the two most common drug class involved in DRPs.

Table 3
types of DRPs identified in the study subjects, HFSTH, Harar, Ethiopia

Types of DRP	Definition of DRPs identified	Frequency	%DRP
Unnecessary drug	Drug therapy is unnecessary because the patient does not have a clinical indication at this time.	69	30.8
• Multiple drug product used		40	57.97
• No valid indication		29	42.03
Need additional drug therapy	Additional drug is required to treat or prevent a medical condition or illness from developing.	53	23.66
• Required additional drug		35	66.03
• Preventive drug therapy required		7	13.21
• Synergistic drug required		11	20.76
Ineffective drugs	The drug product is not being effective at producing the desired response or outcome.	39	17.4
• Drug product is infective		25	64.1
• Inappropriate Dosage form		9	23.07
• Medical condition is refractory		3	12.83
Dose to low	The dosage is too low to produce the desired response or outcome.	33	14.73
• Dose is low to produce optimum outcome		15	45.45
• prolonged dosing interval		7	21.21
• Drug interaction		2	6.06
• Short duration of treatment		9	27.28
Dose to high	The dosage is too high, resulting in undesirable toxic effects	26	11.6
• High dose		10	38.46
• Drug interaction		3	11.53
• Short dosing interval		7	26.93
• Long duration of therapy		9	23.08

Types of DRP	Definition of DRPs identified	Frequency	%DRP
ADR • Patient experienced allergy • Drug is contraindicated	The drug is causing an adverse reaction.	4	1.81
		1	25.00
		3	75.00
DRP	Yes	224	58.3
	No	160	41.7
Number of DRPs /patient	1	125	58.8
	2	82	36.6
	3 ≥	17	4.6
DRP: drug related problem; ADR: adverse drug reaction			

Incidence And Types Of Complications

Of the total number of participants, 121(31.51%: 26.8-35.9) of them were developed different types of BM related complications (Table 1). Of this, seizure (34.71%) followed by comma (16.71%) and the least type of complication was hearing impairment (figure 1).

Factors associated with BM related complication

We performed univariate analysis on the row data set followed by multivariate regression analysis to identify predictive for complication. Age, gestational age, co-morbidity, duration of illness and fever before antibiotics initiation, DRP, length of hospital stay, admission CSF glucose and protein were a candidate variable for multivariate binary logistic regression analysis (p-value<0.25).

After adjusting confounding variables, five factors were significantly associated with the ABM complication. Patient age(AOR=0.01, 95%CI: 0.13-0.19, p=0.024), co-morbidity(AOR=13.18, 95%CI: 1.81-5.6, p<0.001), admission CSF protein(AOR=9.88, 95%CI:9.81.9-96, p=0.002) and DRP(AOR=6.26, 95%CI: 3.58-10.93, p=0.01) were significantly determined the occurrence of complication. Whereas LHS, gestational age CSF glucose and neutrophill and duration of illness before antibiotics initiation were not associated in multivariate regression model (Table 4).

Table 4

Bivariate and multivariate analysis for predictors of ABM related complication at HFSTH, Harar, Ethiopia

Variables		Complication (%)		Bivariate analysis		Multivariate analysis	
		Yes	No	COR(CI)	p-value	AOR(CI)	P-value
Sex	Male	74(61.15)	140(53.24)	0.799(0.516-1.24)	0.313		
	Female	47(38.85)	123(46.76)	1.00	1.00		
Age	Mean±SD	5.01±0.19		0.16(0.13-0.982)	0.072	0.101(0.13-0.19)	0.024
Gestational age	Mean±SD	36.38±2.48		1.19(0.944-1.51)	0.138	1.13(0.86-1.49)	0.385
Co-morbidity	Yes	98(80.99)	88(33.46)	3.65(2.3-0.57)	<0.001	3.18(1.81-5.6)	<0.001
	No	23(19.01)	175(66.54)	1.000	1.00	1.00	1.00
Immunization status	Fully immunized	58(47.93)	78(29.65)	1.55(0.72-3.33)	0.268		
	Partially	15(12.39)	50(19.01)	1.88(0.786-4.5)	0.156		
	Not immunized	38(31.4)	110(41.83)	1.35(0.63-2.87)	0.44		
	Not known	10(8.28)	25(9.51)	1.00	1.00		
Duration of illness before antibiotics initiation	Mean±SD	2.62±1.07		1.16(0.94-1.4)	0.157	2.38(1.73-11.32)	0.009
Temperature at admission	Mean±SD	38.6±0.51		0.81(0.53-1.23)	0.33		
Duration of fever before antibiotics initiation	Mean±SD	2.3±0.94		1.21(0.95-1.54)	0.116	1.18(0.84-1.66)	0.33
Meningitis acquired from	Hospital	6(4.96)	10(3.8)	0.72(0.23-2.26)	0.57		
	Community	115(95.04)	253(96.2)	1.00	1.00		
Admission neutrophill count	Mean ± SD	68.06±15.8		0.99(0.97-1.00)	0.165	0.98(0.97-1.05)	0.093
Admission CSF glucose	Mean ± SD	45.72±11.34		1.01(0.99-1.03)	0.175	0.99(0.97-1.02)	0.45

COR: crude odds ratio, AOR: adjusted odds ration, CSF: Cerebro-spinal fluid, LHS: length of hospital stays ; SD:

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Variables		Complication (%)		Bivariate analysis		Multivariate analysis	
		Yes	No	COR(CI)	p-value	AOR(CI)	P-value
Admission CSF protein	Mean ± SD	60.5±4.53		4.9(2.8-11.92)	0.003	9.38(9.81-9.96)	0.002
Steroid initiated	Yes	74(61.16)	253(96.2)	0.91(0.49-1.68)	0.77		
				1.00			
	No	47(38.84)	10(3.8)		1.00		
DRP	Yes	88(72.72)	136(51.71)	5.6(3.54-8.72)	0.025	6.26(3.58-10.93)	0.01
	No	33(27.28)	127(48.29)				
LHS	Mean ± SD	10.12±3.45		0.98(0.93-1.03)	0.09	0.95(0.88-1.025)	0.19
COR: crude odds ratio, AOR: adjusted odds ration, CSF: Cerebro-spinal fluid, LHS: length of hospital stays ; SD: standard deviation							

Discussion

To the best of our knowledge, this is one of the first studies that evaluated the association between DRP and ABM complications in clinical practice of hospitalized children. In the current prospective observational study, we found that 58.33 % of patients had been exposed to at least one type of DRP. This figure showed that there should be special strategies to prevent DRP and associated complications. These could be continuous patient evaluation or medication reconciliation. The current finding is nearly comparable with the previous study done at Jimma University Medical Center(13) and Vetnam(14). However, this result is lower than the previous finding at Jimma University specialized hospital(15). This difference might be, the previous study was done before the clinical pharmacy service was implemented (5 years ago) and in addition, it incorporates additional errors beyond the seven DRPs including medication reconstitution, dilution and administration technique errors that can significantly increases the number of patients exposed to medication errors. This study also slightly lower than the previous study done at Tikur Anbessa Specialized Hospital(16) 68% had DRP. The difference might be due to study set up. The previous study was done at oncology ward where dose calculation is based on body surface area and prolonged duration of treatment that lead to a diverse type of DRPs. However, our finding is almost 2 times as compared to the previous study in Addis Ababa(17).

Near to sixty percent of patients had one type of DRP where as less than 5% of the study participants were exposed to more than two DRPs. Unnecessary drug, need additional drug and ineffective drug were the three top common DRPs identified in the current study. Of the total patients who were exposed to DRPs, 71.86% children exposed to indication problem. Similar study was found in Vetnam(14). However, the current study is more than

double than what was reported in India(18) only 33.33% was associated drug choice problem. The difference might be associated with the difference in study setting, composition, intra and interprofessional integration and experience of health care professionals towards medication reconciliation. The current study is conducted where clinical pharmacy service is not recognized and integration of inter health care provider is negligible as compared to the previous study. This implied that indication problems might result in reduced efficacy, suboptimum treatment outcome and BM related complications and incremental health care costs (ie complication treatment and for prolonged hospital stay). Dose calculation related (dose to high or dose to low) was the top ranking DRPs at Tikur Anbessa specialized Hospital(16) which is not go hand in hand. The difference could be in the previous report, the dose is based on body surface area that can lead to DRPs.

Children can posed a unique set of risks of DRPs, because of the need for dose calculations that is individually, based on the patient's weight, age or body surface area, and need of medication dilution. In the current study, dosing related DRPs was accounted about 26% (almost equal share of dose to low and dose to high). Nearly similar result was reported previously done at Jimma University specialized hospital (14) in which 23% was associated with dosing error. This finding suggested that health care professionals in this setup shall be conscious enough on dose calculation.

In this study, we investigated different types of complication including seizure, comma, hearing impairment, hydrocephalus and others. Seizure (34.71%) is most common neurological complication. Study(19) showed similar complications including; seizure, hydrocephalus, hearing impairment and movement disorder were the most common complications among patients with poor prognosis. This finding suggested that the health care providers shall be conscious when evaluate patients with meningitis and ready to treat seizure for short term (i.e depending on the presence of risk factors and duration and frequency of seizure). Another comparable result was also reported from the previous study done in Finland and Taiwan(20–21) in which seizure was the top ranking neurological squeal. However, the rate of neurological complication incidence in our study is higher (31.51%) as compared to the previous studies(20, 22–24). This high incidence rate in our study might be associated with delayed hospital presentation, availability of effective medication, difference in medical, nursing and pharmaceutical care services even after admission.

In this study, we computed multivariate analysis and indicated that five variables were independently affect the occurrence of BM related complication. Significant association was noted between patient age and complications. As age increased by one unit, incidence of complication was reduced by 10%. Similar study was found (25–27). The chance of BM related complication might be low due to immune development as age increases. We also found significant association between long duration of illness before antibiotics initiation and complication. As the health care professionals delayed one extra unit to initiate antibiotics, the patient had more than 2 times to develop complication. This finding is important to ignite health care professionals to initiate antibiotics as soon as possible. As duration of illness without intervention increases, high probability of cell death due to persistent fever (killer). The same finding was reported (25). Children, who had at least one additional disease condition, more than three times more likely develop complication as compared to who are free from co-morbidity. This might be as the presence of disease conditions increased, there could be increased the number of medication and, however, inappropriately treated lead to additional opportunity to develop complication. Prospective observational studies (28–31) identified that elevation of CSF protein was significantly associated with complications; the present study also support the previous finding. As one unit increment of CSF protein, the child is more than 9 times more prone to develop complication. However, CSF glucose has no negative impact in

our study in multivariate model. DRP was included in multivariate binary logistic regression analysis model. BM related complication was more common in children who had DRP as compared to children who have no DRP (AOR=6.26, 95%CI: 3.58-10.93, p=0.01).

In our study both immunization status and the use of adjuvant corticosteroids has no association with complication. The use of adjuvant corticosteroids has no association with neurological complication. The previous finding (32) support the current study; adjuvant corticosteroid therapy was not associated with time to death, acute complication or time to hospital discharge. However, a retrospective analysis(33) reported that adjuvant corticosteroid use and immunization status were associated with BM associated complication. Since the previous report was absolutely depend on secondary data that might make a difference. In addition, in our study, the analysis was not computed for only hearing impairment; however, the previous study was evaluated for only hearing impairment.

Limitation

although, this is a prospective and the first study that tried to evaluate the impact of DRPs on BM complications, it is not without limitation. This study is single center study and the result and conclusion might not be externalized

Conclusion

The present study demonstrated that more than half of the hospitalized children with meningitis had at least one DRP. Significant proportion of admitted children developed BM related complications. Significant association between DRP and complication was identified. Patient age, CSF protein, delayed antibiotics initiation and co-morbidity were significantly associated with the occurrence complication. Health professional shall start antibiotics as soon as possible, the hospital should develop medication reconciliation strategies, and a pediatric dosing chart to prevent DRP and associated complications.

Abbreviations

BM
bacterial meningitis
SD
standard deviation
LP
lumbar puncture
CSF
Cerebrospinal fluid
HFSTH
Hiwot Fana Specialized Teaching Hospital
COR
crude odds ratio
AOR
adjusted odds ratio
DRP

LHS
length of hospital stay
ADR
adverse drug reaction

Declarations

The present study was conducted according to the Helsinki declaration (October, 2000). Ethical clearance was obtained from Mizan-Tepi University and sent to HFSH. HFSH approved and allowed to the investigators to collect data from the patient. Written informed consent was given to the parents to interview the patient when appropriate and filter laboratory and drug related data from the patient medical chart.

Consent for publication: both authors are agreed to publish this paper in the current form.

Availability of data and materials: all data are available here for publication.

Competing interest: both authors declared that there is no competing interest.

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Author's contribution: Both authors had valuable contribution for maturation of this paper starting from conceptualization to manuscript preparation and submission. They have also responsibilities for any concern.

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Figures

Figure 1

types of BM related complications at HFSTH, Harar, Ethiopia