Review

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Bacterial profile and multi-drug resistance pattern of bacterial isolates among septicemia suspected cases: a meta-analysis report in Ethiopia

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Abstract

Background: Bloodstream infections (BSIs) are one of the most common infections seen in all age groups and in all locations. The current knowledge on the patterns of bacterial profile, and its antibiotic resistance are essential to design and implement appropriate interventions. This study was conducted to assess the prevalence and multi-drug resistance pattern of bacterial isolates among septicemia and/or bacteremia suspected cases in Ethiopia.

Methods: Searching was conducted in databases of PubMed, Research Gate, Scopus and Google Scholar. In addition, manual searching is also conducted in bibliographies of included studies and in other meta-analysis studies. Required data were extracted from articles published up to 2020 on the bacterial profile of septicemia in Ethiopia, and analyzed using comprehensive meta-analysis version 3.3.0 software.

Results: A total of 5,823 septicemia suspected cases were extracted from 18 included studies and the overall blood culture positive rate of 31.9% (95% CI: 0.261–0.382). Of these, the overall Gram positive and Gram negative isolates was 57.8% (95% CI: 0.534–0.584) and 42.2% (95% CI: 0.416–0.466), respectively. Among Gram positives, predominantly reported isolates was *Staphylococcus aureus* (47.9%: 480 of 1,003), followed by *Coagulase-Negative Staphylococcus* (42.7%: 428 of 1,003), whereas among Gram negatives, the most frequently reported isolates was *Klebsiella* species

(29.8%: 218 of 731), followed by *Escherichia coli* (23.1%: 169 of 731). Significant levels of resistance was reported against ampicillin, amoxicillin, ceftriaxone, co-trimoxazole and tetracycline with a pooled resistance range of 40.6–55.3% in Gram positive and 52.8–85.7% in Gram negative isolates. The pooled estimates of multi-drugs resistance (MDR) was (66.8%) among Gram positives and (80.5%) among Gram negatives, with the overall MDR rate of (74.2%).

Conclusions: The reported blood culture positive rates among septicemia cases were relatively high. Second, the level of drug and multi-drug resistant isolates against commonly prescribed antibiotics was significant. However, the scarcity of data on culture confirmed septicemia cases as well as patterns of antimicrobial resistance may overshadow the problem.

Keywords: antimicrobial resistance (AMR); bacteremia; bacterial profile; Ethiopia.

Background

Bloodstream infections (BSIs) can be sepsis and/or bacteremia and are one of the most common infectious diseases seen in all age groups, and in all locations, with the greatest burden in low-income countries [1]. These infections can be caused by bacterial, viral, fungal, or parasitic infections, and can be mimicked by non-infectious etiologies, making diagnosis particularly challenging where an infectious source is not immediately apparent [1, 2].

The epidemiology of bloodstream infections is different across the world: globally, an estimated of 48.9 million incident cases of septicemia and 11.0 million sepsis-related deaths (representing 19.7% of all global deaths) were reported, in 2017 [2]. Among all age groups, both sexes, and all locations, the most common underlying cause of sepsis was diarrhoeal diseases, with 9.21 million cases of sepsis attributable to diarrhoeal diseases [2]. Studies in Africa suggest that prevalence of bacterial infections among inpatients is greater than that described in wealthier regions [3–5].

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Although, early treatment with appropriate antimicrobials has been shown to reduce morbidity and mortality in cases of bacterial infection, the threat of antimicrobial resistance (AMR) is growing at an alarming rate and the situation is perhaps aggravated in developing countries due to gross abuse in the use of antimicrobials [6, 7]. In addition, the emergency of multi-drug resistance among Gram-negative bacteria is a major concern, given the scarcity of diagnostic microbiology laboratories and difficulty in accessing effective antibiotic therapy for resistant pathogens [8]. For instance, the estimated prevalence of extended-spectrum β -lactamase (ESBL)-producing Enterobacteriaceae in Asia and Sub-Saharan Africa is between 60 and 90% [8], highlighting the growing challenge of treating bloodstream infections in these countries. The increasing use of broad-spectrum antibiotics and lack of good stewardship have contributed to the increasing of these multi-drugs resistance (MDR) organisms that contribute for poor treatment outcome [9, 10].

The diagnostic test that is most often associated with bacterial sepsis is the blood culture [11]. However, in areas without advanced laboratory test, especially in our situation, many infections are treated empirically without microbiological investigation of the etiologic agents. Due to these, the current knowledge on the patterns of bacterial isolates, its antibiotic resistance profile, and associated factors was limited, although it is essential in designing and implementations of appropriate interventions. Therefore, this finding has several key implications for health policy makers, clinicians, and researchers to update infection-prevention measures and to implement in areas with the highest incidence of septicemia and/or bacteremia and among populations on which septicemia will have the greatest impact.

Methods

Study design

A meta-analysis study consisting of different studies on bacterial profile and antimicrobial resistance pattern among of septicemia and/or bacteremia suspected cases of all age group was conducted in Ethiopia. While conducting this meta-analysis, the authors tried to follow Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) flow diagram and checklist (<http://www.prisma-statement.org/>) [12] during the screening of titles and abstracts as well as evaluation of full-texts for eligibility and final inclusion.

Study selections and search strategies

Search was carried out in the database of PubMed, Research Gate, Scopus and Google Scholar. “Bacterial profile”, OR “septicemia”, OR “bacteremia AND antimicrobial resistance”, “bloodstream infection” OR “antimicrobial resistance” OR “Sepsis” OR “antimicrobial resistance” AND “Ethiopia” were used as search strategies. In addition, relevant studies were manually searched from bibliographies of eligible studies and from other meta-analysis studies. All studies conducted in Ethiopia and that available online up to April, 2020, and studies focusing on the bacterial profile with their antimicrobial resistance pattern among septicemia and/or bacteremia suspected cases in all age groups and studies contain sufficient outcome variables were considered as appropriate for eligibility assessment.

Screening and eligibility criteria

All studies conducted outside Ethiopia and those with unrelated outcomes of interest were excluded. First duplicated records were removed and then two authors (MA and SH) were independently inspected all the titles and abstracts of articles related to the study question and those irrelevant articles were excluded. Articles passed the first step were further screened in a second step by reviewing the full-texts and evaluated the eligibility of them for final inclusion (Figure 1). The third author (MA*) adjudicated disagreement arose between the first two reviewers.

Data extraction

Two authors (MA and SH) were independently extracted important outcome variables from each included studies. Data related to first author, study area, region of the study, study periods, year of publication, study design, sample size, target population, and outcome of interests, such as number of patients who had blood cultures sampled, the number who had positive cultures for a bacterial pathogen, number and gram reactions and common species of bacterial pathogen, and proportion and/or number of drug and multi-drug resistant isolates were recorded. Data extractions were made at least twice to remove any discordance and pre-determined and piloted forms were used as data extraction tools.

Outcome variables

The first outcome variable is the blood culture positive rates of bacteremia suspected cases in Ethiopia. The pooled

Figure 1: Flow chart depicting the selection process of included articles.

blood culture positive rate was calculated per sample size (number of patients who had blood cultures sampled). The second outcome variable is antimicrobial resistance profiles and multi-drug resistance patterns of the common bacterial isolates against selected antimicrobials of different categories.

Quality assessment of included studies

Items included in strengthening the reporting of observational studies in epidemiology (STROBE) Statement-checklist [13], were used to check the quality of included studies. The quality scores for each study were calculated against items of the STROBE checklist adequately. There were no limits with regard to study type except that the study had to be an original study. In addition, we didn't exclude any studies based on quality.

Data processing and analysis

A meta-analysis was done to calculate the culture positive rate of septicemia and/or bacteremia suspected cases, the

proportional representation of Grams positive and Grams negative pathogen and the pooled estimates of drug and multi-drug resistance isolates using comprehensive meta-analysis version 3.3.0 software (www.Meta-analysis.com). A random-effect meta-analysis model was used to assess the outcome variables and variability of included studies and significant variation was considered at p-values <0.05 and $I^2 > 50\%$. A Begg's and Egger's test was performed to assess publication bias and statistical significant evidence was considered at p-value <0.05.

Results

Search results and selection process of included articles

Two hundred sixty nine (269) studies regarding septicemia in all age group were identified from PubMed, Research Gate, Scopus, Google Scholar and other sources. Among these, 28 articles were enrolled for abstract and title screen. After full text assessment of 25 articles, 18 articles fulfilled the inclusion criteria were included for meta-analysis (Figure 1).

Table 1: Characteristics of studies included in meta-analysis of the culture positive rates of sepsis cases in Ethiopian.

Study region	Study area	Study period	Study design	Publication year	Study population	Sample size	Culture positives cases, n (%)	References
Amhara	Gondar	September 2015 to May 2016	Cross-sectional	2017	0–28 days	251	117 (46.6%)	G/eyesus et al. [14]
	Gondar	September 2006 to January 2012	Cross-sectional	2013	All age groups	390	71 (18.2%)	Dagnaw et al. [15]
	Gondar	July 2011 to June 2012	Cross-sectional	2012	1–28 days	181	58 (32.1%)	Gebrehiwot et al. [16]
	Gondar	March to May 2013	Retrospective cross-sectional	2018	All age groups	856	169 (19.7%)	Ababaw et al. [17]
Oromia	Bahir Dar	March 2013 to January 2015	Cross-sectional	2016	All age groups	561	220 (39.2%)	Hailu et al. [18]
	Gondar	March to May 2013	Cross-sectional	2016	HIV patients	100	31 (31%)	Alebachew et al. [19]
	Gondar	March 2001 to April 2005	Cross-sectional	2008	All age groups	472	114 (24.2%)	Ali and Kebede [20]
	Gondar	February to April 2017	Cross-sectional	2018	All age groups	216	42 (19.4)	Fentie et al. [21]
	Bahir Dar	January to May 2017	Cross-sectional	2020	Post-partum/Aborted women	166	56 (33.7%)	Admas et al. [22]
	Asella	April 2016 to May 2017	Cross-sectional	2019	0–28 days	303	88 (29.4%)	Sorsa et al. [23]
Central Ethiopia	Jimma	April to October 2018	Cross-sectional	2020	0–28 days	238	135 (56.7%)	Gashaw et al. [24]
	Jimma	March to June 2013	Cross-sectional	2016	All age groups	95	15 (15.8%)	Kumalo et al. [25]
	Addis Ababa	October 2011 to February 2012	Cross-sectional	2015	1 day–12 years	201	56 (27.9%)	Negussie et al. [26]
	Addis Ababa	October 2006 and March 2007	Cross-sectional	2010	0–28 days	302	135 (44.7%)	Shitaye et al. [27]
	Addis Ababa	2007–2008	Cross-sectional	–	0–28 days	578	166 (28.7%)	Yusuf and Worku [28]
	Addis Ababa	December 2011 to June 2012	Cross-sectional	2018	≥18 years	107	76 (71.0%)	Arega et al. [29]
	Addis Ababa	August 2012 to October 2013	Cross-sectional	2015	All age groups	292	38 (13.0%)	Seboxa et al. [30]
	Mekelle	March to October 2014	Cross-sectional	2015	All age groups	514	144 (28.0%)	Wasihun et al. [31]
Tigray								

Characteristics of included studies

All included studies (18) were hospital-based cross-sectional study design and published in the year from 2008 to 2020. All studies utilized blood specimens for detection of bacterial causes of sepsis, and were conducted among inpatient and/or outpatients as their sources of samples. Half of 9 (50.0%) [14–22] the included articles were conducted in the Amhara region of Ethiopia, 3 (16.7%) [23–25] in Oromia region, 5 (27.8%) [27–31] were in central Ethiopia (Addis Ababa) and only 1 (5.6%) [31] study conducted in Tigray region of Ethiopia. With regard to study population, 9 (50%) [15, 17–21, 25, 30, 31] of included studies included all age groups as their study subjects, 6 (33.3%) [14, 16, 23, 24, 27, 28] focused on neonates, each of 1 (5.6%) study was focused

on post-partum/aborted women [22], 1 day–12 years [26] and age group of ≥ 18 years [29]. The highest and the lowest proportion of culture positive sepsis cases were reported from central Ethiopia, with respective proportions of 71.0% [29] and 13.0% [30] (Table 1). The median score of studies against STROBE items was 67.2% with a range of 41.5–79.4.

Publication bias

Non-significant effect of publication bias was observed among included studies with a Begg’s and Egger’s p-value > 0.05 (Figure 3). But, Begg’s suggested that a non-significant correlation may be due to low statistical power, and cannot be taken as evidence that bias is absent.

Figure 2: Overall blood culture positive rate of septicemia cases in different region of Ethiopia.

Figure 3: Funnel plot depicting publication bias of studies reporting the bacterial profiles causing septicemia and/or bacteremia in different parts of Ethiopia.

Culture positive rates of septicemia cases in Ethiopia

This study, the overall estimated culture positive bacteremia and/or sepsis case was 31.9% with a confidence interval of (95% CI: 0.261, 0.382). The pooled proportions of culture

positive bacteremia and/or sepsis cases was estimated by using a random and fixed effect model and overall significant heterogeneity was observed between the studies ($I^2=95.5\%$; $p\text{-value} \leq 0.001$) (Figure 2). The variation in the study setups, study periods, and study populations, could have an effect on the severity of heterogeneity among the included studies.

Table 2: Summary of studies included regarding the most common isolated bacterial species causing sepsis in Ethiopian.

First authors [references]	Total # of isolates	Commonly detected species of bacteria	
		Gram positives	Gram negatives
G/eyesus et al. [14]	120	81 (67.5%) CoNs = 26, <i>S. aureus</i> = 49, <i>S. pyogenes</i> = 6	39 (32.5%) <i>K. pneumoniae</i> = 19, <i>E. coli</i> = 12, <i>Serratia</i> = 1, <i>E. cloacae</i> = 4 and <i>K. rhinose</i> = 3
Dagneu et al. [15]	71	49 (69%) CoNs = 30, <i>S. aureus</i> = 17, Other = 2	22 (31%) <i>Klebsiella</i> spps = 9, <i>E. coli</i> = 5, Others = 8
Gebrehiwot et al. [16]	58	22 (37.9%) CoNs = 4, <i>S. aureus</i> = 17, Other = 1	36 (62.1%) <i>Klebsiella</i> spps = 16, <i>E. coli</i> = 6, Others = 12
Abebaw et al. [17]	174	112 (64.4%) CoNs = 55, <i>S. aureus</i> = 48, <i>S. pyogenes</i> = 6, Other = 3	62 (35.6%) <i>Klebsiella</i> spps = 11, <i>E. coli</i> = 15, <i>Citrobacter</i> spps = 8, Others = 28
Hailu et al. [18]	220	105 (47.7%) CoNs = 35, <i>S. aureus</i> = 50, <i>E. faecalis</i> = 6, Other = 14	115 (52.3%) <i>K. pneumoniae</i> = 35, <i>E. coli</i> = 19, <i>P. aerugi-</i> <i>nosa</i> = 15, <i>Proteus</i> spps = 6, Others = 40
Alebachew et al. [19]	31	26 (83.9%) CoNs = 8, <i>S. aureus</i> = 13, Other = 5	5 (16.1%) <i>K. ozaenae</i> = 1, <i>E. coli</i> = 1, Others = 3
Ali and Kebede [20]	114	80 (70.2%) CoNs = 38, <i>S. aureus</i> = 34, Other = 6	34 (29.8%) <i>Klebsiella</i> spps = 10, <i>E. coli</i> = 2, Others = 19
Fentie et al. [21]	43	25 (58.1%) CoNs = 11, <i>S. aureus</i> = 12, Other = 2	18 (41.9%) <i>Klebsiella</i> spps = 2, <i>E. coli</i> = 9, Others = 7
Admas et al. [22]	56	23 (41.1%) CoNs = 4, <i>S. aureus</i> = 19, Other = 0	33 (58.9%) <i>Klebsiella</i> spps = 7, <i>E. coli</i> = 18, Others = 8
Sorsa et al. [23]	88	49 (55.7%) CoNs = 22, <i>S. aureus</i> = 16, <i>Enterococcus</i> spps = 6, <i>S. pneumoniae</i> , <i>L. monocytogenes</i> and <i>Candida</i> = 5	39 (44.3%) <i>Klebsiella</i> spps = 11, <i>E. coli</i> = 18, <i>Enterobacter</i> spps = 6, <i>Citrobacter</i> spp = 4
Gashaw et al. [24]	135 bacteria & eight fungi	70 (51.8%) CoNs = 36, <i>S. aureus</i> = 27, Other = 7	65 (48.2%) <i>Klebsiella</i> spps = 21, <i>E. coli</i> = 5, Others = 39
Kumalo et al. [25]	15	8 (53.3%) CoNs = 2, <i>S. aureus</i> = 6, Other = 0	7 (46.7%) <i>Klebsiella</i> spps = 1, <i>E. coli</i> = 1, Others = 5
Negussie et al. [26]	55 bacteria + one fungi	26 (46.4%) CoNs = 11, <i>S. aureus</i> = 13, Other = 2	29 (51.8%) <i>Klebsiella</i> spps = 9, <i>E. coli</i> = 1, <i>Serratia mar-</i> <i>censcens</i> = 12, Others = 7
Shitaye et al. [27]	135	59 (43.7%) CoNs = 10, <i>S. aureus</i> = 30, Other = 19	76 (56.3%) <i>Klebsiella</i> spps = 50, <i>E. coli</i> = 10, Others = 16
Yusuf and Worku [28]	166	104 (62.7%) CoNs = 69, <i>S. aureus</i> = 37, Other = 9	62 (37.3%) <i>Klebsiella</i> spps = 11, <i>E. coli</i> = 15, Others = 36
Arega et al. [29]	71 bacteria + 11 fungi	43 (60.5%) CoNs = 12, <i>S. aureus</i> = 31, Other = 0	28 (39.5%) <i>Klebsiella</i> spps = 3, <i>E. coli</i> = 1, Others = 24
Seboxa et al. [30]	38	18 (47.4%) CoNs = 11, <i>S. aureus</i> = 7, Other = 0	20 (52.6%) <i>Klebsiella</i> spps = 1, <i>E. coli</i> = 15, Others = 2
Wasihun et al. [31]	144	103 (71.5%) CoNs = 44, <i>S. aureus</i> = 54, Other = 5	41 (28.5%) <i>Klebsiella</i> spps = 1, <i>E. coli</i> = 16, Others = 25
Total, n (%; 95% CI)	1,734	1,003 (57.8%; 0.534, 0.584)	731 (42.2%; 0.416, 0.466)

CoNs, *Coagulase-Negative Staphylococcus*; CI, confidence interval; Other: *Pseudomonas* spps, *Serratia* spps, *Enterobacter* spps, *Citrobacter* spps, *Acinetobacter* spps, *Streptococci* spps, *Enterococcus* spps, *Listeria* spps, *Salmonella* spps and fungi.

Bacterial profiles causing bacteremia in Ethiopia

In this study, from a total of 5,823 patients suspected of bacteremia, 1,734 were confirmed to be positive for blood culture. Of these, the overall reported Gram positive and Gram negative isolates was 57.8% (95% CI: 0.534, 0.584) and 42.2% (95% CI: 0.416, 0.466), respectively (p-value=1.000). Among Gram positives, the most predominant reported isolates was *Staphylococcus aureus* (47.9%: 480 of 1,003 Gram positives), followed by *Coagulase-Negative Staphylococcus* (42.7%: 428 of 1,003 Gram positives). Among Gram negatives, the most frequently reported isolates was *Klebsiella* species with a rate of 29.8% (218 of 731 Gram negatives), followed by *Escherichia coli* with the proportion of 23.1% (169 of 731 Grams negatives) (Table 2).

Antimicrobial resistance profiles of bacterial isolates

In this study, antimicrobial resistance profiles of the extracted Gram-positive and Gram-negative bacteria were analyzed against few selected antibiotics and have been presented in Table 3. Accordingly, among Gram positive and Gram negative isolates, high resistant rates were observed against ampicillin (55.3%; 95% CI: 0.455, 0.646) and (85.7%; 95% CI: 0.801, 0.900) and amoxicillin (40.6%; 95% CI: 0.348, 0.488) and (57.4%; 95% CI: 0.493, 0.651), respectively. The pooled proportion of resistance against ceftriaxone was 43.3% (95% CI: 0.338, 0.533) and 52.8% (95% CI: 0.408, 0.645), respectively. Resistance rate of Gram positive and Gram negative isolates against cotrimoxazole was 52.6% (95% CI: 0.403, 0.646) and 60.3% (95% CI: 0.515, 0.864) and against tetracycline was 49.1% (95% CI: 0.311, 0.675) and 69.5% (95% CI: 0.529, 0.822), respectively. Both Gram positive and Gram negative isolates recorded with lower levels of resistance against ciprofloxacin 23.8% (95% CI: 0.185, 0.299) and 22.4% (95% CI: 0.166, 0.296) and gentamycin 32.4% (95% CI: 0.229, 0.436) and 44.2% (0.314, 0.579), respectively.

Multi-drugs resistance (MDR) profiles of bacterial isolates

In this study, the pooled proportional estimates of MDR Gram positive isolates was found to be 66.8% (95% CI: 0.556, 0.759), whereas among Gram negative isolates MDR was found to be 80.5% (95% CI: 0.672, 0.888). The overall MDR rate was 74.2% (95% CI: 0.640, 0.823) (Table 4).

Discussion

Bacterial profile of septicemia is constantly changing thus, current knowledge on the patterns of bacterial isolates, its antibiotic resistance profile, and associated factors, are essential to design and implement appropriate interventions. It is the first a meta-analysis study conducted to determine pooled prevalence of blood culture positive rate of septicemia and/or bacteremia suspected cases and bacterial profiles with their antimicrobial resistance in Ethiopia. Accordingly, in this meta-analysis, the overall estimated rate of positive blood culture was (31.9%), which is in agreement with other finding in developing countries [32–34]. However, this finding is relatively higher [35–39], and lower [40–42] than a study findings from low- and middle-income countries.

Although, laboratory confirmed blood culture remains the best approach and the gold standard measure to identify microorganisms when a bloodstream infection is suspected, to guarantee that the antimicrobial treatment is adequate [43, 44], the limited number of studies in African regions, including Ethiopia with laboratory confirmed cases would underestimate the prevalence of sepsis in this meta-analysis. Rapid microbiological investigations of the causative agent with their antimicrobial susceptibility testing (AST) are very important to adjust the anti-infectious therapy and to avoid inefficient treatment, to reduce the spectrum of the anti-infectious therapy so as to limit the selection of resistant strains [11]. However, the population screened for bloodstream infections often may not have bacterial infection, and those that do may not be detectable with blood cultures. This is because of unavailability and sensitivity and specificity of blood culture is overall low, partly because it depends on the blood volume drawn, the timing of the blood draw, any prior treatment with antibiotics, and the presence of viable organisms [45, 46].

In this meta-analysis, the overall prevalence for Grams positive and Grams negative isolates was 57.8 and 42.2%, respectively. The higher prevalence of Gram negative than Grams positive isolates was reported in low- and middle-income and developed countries [38, 43, 47, 48]. In contrast, higher prevalence of Gram positive than Grams negative isolates was reported in Egypt and China [42, 49]. In this study, the most predominant reported Gram positives and Gram negatives isolates was *S. aureus* (47.9%), CoNs (42.7%), *Klebsiella* spp (29.8%) and *E. coli* (23.1%). The predominance of the above isolates as common causes of septicemia was also reported in many previous studies [34, 38, 49]. Another large systematic review on causative pathogens of community-acquired sepsis in low- and

Table 3: Pooled antibiotic resistance rates of bacteria causing septicemia in Ethiopia.

First authors [references]	Gram reactions of isolates	Antibiotic resistance profiles, n (%)							
		AMP	AMX	CRO	CN	CIP	SXT	TE	
G/eyesus et al. [14]	GP=81	30/81 (37.0)	-	22/81 (27.2%)	28/81 (34.6)	16/81 (19.8)	34/81 (42.0)	28/81 (34.6)	
	GN=39	33/39 (84.6)	11/39 (28.2)	22/39 (56.4%)	5/39 (17.2)	5/39 (12.8)	17/39 (43.6)	10/39 (25.6)	
	GP=49	33/49 (67.4)	-	29/49 (59.2%)	27/49 (55.1)	13/49 (26.5)	31/49 (63.3)	-	
	GN=39	28/39 (71.8)	-	-	27/39 (69.2)	11/39 (28.2)	24/39 (61.5)	-	
Negussie et al. [26]	GP=26	24/26 (92.3)	-	10/26 (38.5)	9/26 (34.6)	6/26 (23.1)	17/26 (65.4)	14/26 (53.8)	
	GN=29	29/29 (100)	-	19/29 (65.5)	26/29 (89.7)	4/29 (13.8)	25/29 (86.2)	23/29 (79.3)	
	GP=49	20/49 (40.8)	13/49 (26.5)	17/47 (36.2)	14/47 (29.9)	12/47 (25.5)	26/47 (55.3)	28/47 (59.6)	
	GN=22	17/22 (77.3)	10/22 (45.5)	10/22 (45.4)	7/22 (31.8)	6/22 (27.3)	11/22 (50.0)	13/22 (59.1)	
Gebrehiwot et al. [16]	GP=22	17/22 (77.3)	6/22 (27.3)	16/22 (72.7)	-	11/22 (50.0)	18/21 (85.1)	19/21 (90.5)	
	GN=36	35/36 (97.2)	1/36 (2.8)	21/36 (58.3)	-	14/34 (41.2)	12/17 (70.6)	22/33 (66.7)	
	GP=59	22/59 (37.3)	16/59 (27.1)	10/59 (16.9)	12/59 (20.3)	0	6/59 (10.2)	-	
	GN=76	70/70 (100)	53/70 (75.7)	65/70 (92.9)	65/70 (92.9)	2/70 (2.9)	34/70 (48.6)	-	
Abebaw et al. [17]	GP=112	71/112 (63.4)	64/112 (57.1)	44/109 (40.4)	49/112 (43.8)	36/111 (32.4)	-	-	
	GN=62	56/62 (90.3)	55/62 (88.7)	19/61 (31.2)	33/58 (56.9)	18/58 (31.0)	38/61 (62.3)	46/62 (74.2)	
	GP=105	83/105 (79.1)	-	48/105 (45.7)	71/105 (67.6)	25/105 (23.8)	68/105 (64.8)	-	
	GN=61	-	-	-	-	-	-	-	
Hailu et al. [18]	GP=105	46/85 (54.1)	-	-	1/6 (16.7)	13/90 (14.4)	23/88 (26.1)	6/86 (7.0)	
	GN=115	95/115 (82.6)	-	68/100 (68.0)	60/115 (52.2)	24/115 (20.9)	66/100 (66.0)	-	
	GP=26	17/26 (65.4)	0	0	3/26 (11.5)	1/26 (3.8)	17/26 (65.4)	8/26 (30.8)	
	GN=5	5/5 (100)	4/5 (80.0)	1/5 (20.0)	1/5 (20.0)	0	5/5 (100)	4/5 (80.0)	
Gashaw et al. [24]	GP=70	-	-	50/70 (71.4)	-	-	60/70 (85.7)	54/70 (77.1)	
	GN=65	65/65 (100)	65/65 (100)	54/65 (83.1)	35/65 (53.8)	26/65 (40.0)	47/65 (72.3)	56/65 (85.2)	
	GP=103	-	13/103 (12.6)	54/103 (52.4)	26/103 (25.4)	34/103 (33.0)	77/103 (74.8)	-	
	GN=41	-	4/41 (7.8)	21/41 (51.2)	8/41 (19.5)	3/41 (7.3)	12/41 (29.3)	-	
Arega et al. [29]	GP=43	16/43 (37.2)	27/43 (62.8)	29/43 (67.4)	-	-	13/43 (30.3)	19/43 (44.2)	
	GN=28	18/24 (75.0)	20/24 (83.3)	11/24 (45.8)	5/24 (20.8)	3/24 (12.5)	19/24 (79.2)	11/24 (45.8)	
	GP=25	-	-	-	5/25 (20.0)	7/25 (28.0)	10/25 (40.0)	5/25 (20.0)	
	GN=18	15/18 (83.3)	14/18 (77.8)	4/18 (22.2)	5/18 (27.8)	5/18 (27.8)	-	-	
Seboxa et al. [30]	GP=18	-	0	1/7 (14.9)	0	0	3/7 (42.9)	-	
	GN=20	-	7/20 (35.0)	9/20 (57.1)	9/20 (45.0)	8/20 (40.0)	13/20 (65.0)	-	
	GP=23	12/23 (52.2)	-	4/23 (17.4)	-	3/23 (13.0)	8/23 (34.8)	23/23 (100)	
	GN=33	33/33 (100)	18/33 (54.6)	16/33 (48.5)	7/33 (21.2)	8/33 (24.2)	16/33 (48.5)	31/33 (93.9)	
Kumalo et al. [25]	GP=8	6/8 (75.0)	2/8 (25.0)	1/8 (12.5)	0	1/8 (12.5)	0	5/8 (62.5)	
	GN=7	6/7 (85.7)	1/7 (14.9)	4/7 (57.1)	2/7 (28.6)	1/7 (14.9)	4/7 (57.1)	5/7 (71.4)	
	Pooled resistance rate, % (95% CI)	GP	55.3 (0.455, 0.646)	40.6 (0.348, 0.488)	43.3 (0.338, 0.533)	32.4 (0.229, 0.436)	23.8 (0.185, 0.299)	52.6 (0.403, 0.646)	49.1 (0.311, 0.675)
		GN	85.7 (0.801, 0.900)	57.4 (0.493, 0.651)	52.8 (0.408, 0.645)	44.2 (0.314, 0.579)	22.4 (0.166, 0.296)	60.3 (0.515, 0.864)	69.5 (0.529, 0.822)
Combined resistance rate, % (95% CI)		73.0 (0.657, 0.792)	47.5 (0.428, 0.523)	47.9 (0.401, 0.559)	39.9 (0.314, 0.490)	-	57.7 (0.499, 0.652)	55.2 (0.380, 0.712)	

NB, not analyzed; GP, Gram positives; GN, Gram negatives; AMP, ampicillin; AMX, ampicillin; CRO, ceftriaxone; CN, gentamycin; CIP, ciprofloxacin; SXT, trimethoprim-sulphamethoxazole; TE, tetracycline; CI, confidence interval.

Table 4: Pooled multi-drug resistance (MDR) rates of bacteria causing septicemia in Ethiopia.

First authors [references]	Total MDR	Gram reaction of isolates	# of MDR	Pooled MDR rate, % (95% CI)
G/eyesus et al. [14]	78/120 (65%)	Gram positives (n=81)	56/81	69.1 (0.583, 0.782)
		Gram negatives (n=39)	22/39	56.4 (0.709, 0.425)
Sorsa et al. [23]	63/88 (72%)	Gram positives (n=49)	32/49	65.3 (0.511, 0.772)
		Gram negatives (n=39)	31/39	79.5 (0.640, 0.894)
Negussie et al. [26]	51/55 (92.7%)	Gram positives (n=26)	25/26	96.2 (0.772, 0.955)
		Gram negatives (n=29)	26/29	89.7 (0.724, 0.964)
Gebrehiwot et al. [16]	52/58 (85.7%)	Gram positives (n=22)	19/22	86.4 (0.652, 0.955)
		Gram negatives (n=36)	33/36	91.7 (0.771, 0.973)
Shitaye et al. [27]	91/135 (67.4%)	Gram positives (n=59)	27/59	45.8 (0.336, 0.585)
		Gram negatives (n=76)	64/76	84.2 (0.742, 0.908)
Abebaw et al. [17]	151/174 (86.9%)	Gram positives (n=112)	94/112	83.9 (0.759, 0.896)
		Gram negatives (n=62)	57/62	91.9 (0.820, 0.966)
Alebachew et al. [19]	25/31 (80.6%)	Gram positives (n=26)	21/26	80.8 (0.613, 0.918)
		Gram negatives (n=5)	4/5	80.0 (0.309, 0.973)
Gashaw et al. [24]	114/135 (84.4%)	Gram positives (n=70)	51/70	72.9 (0.613, 0.820)
		Gram negatives (n=65)	63/65	96.9 (0.885, 0.992)
Wasihun et al. [31]	85/144 (59.0%)	Gram positives (n=103)	64/103	62.1 (0.524, 0.710)
		Gram negatives (n=41)	21/41	51.2 (0.363, 0.660)
Arega et al. [29]	19/71 (26.9%)	Gram positives (n=43)	13/43	30.2 (0.184, 0.454)
		Gram negatives (n=28)	6/16	37.5 (0.179, 0.623)
Fentie et al. [21]	20/43 (46.5%)	Gram positives (n=25)	10/25	40.0 (0.230, 0.597)
		Gram negatives (n=18)	10/18	55.0 (0.330, 0.760)
Admas et al. [22]	47/56 (83.9%)	Gram positives (n=23)	14/23	60.9 (0.402, 0.782)
		Gram negatives (n=33)	33/33	98.5 (0.804, 0.999)
Kumalo et al. [25]	12/15 (80.0%)	Gram positives (n=8)	7/8	87.5 (0.312, 0.764)
		Gram negatives (n=7)	5/7	71.4 (0.321, 0.542)
Total MDR rate % [95% CI]		Gram positives (n=647)	433	66.90 (0.556, 0.759)
		Gram negatives (n=478)	375	80.50 (0.672, 0.888)
Combined MDR rate % [95% CI]		GP 'plus' GN=1,125	808	74.20 (0.640, 0.823)

GP, Gram positives; GN, Gram negatives; MDR, multi-drug resistance; CI, confidence interval.

middle-income countries demonstrated that, the most prevalent bacterial pathogens for neonatal sepsis as *S. aureus*, *E. coli*, and *Klebsiella* species [50, 51].

With regard to AMR, in this study, the pooled proportion of MDR Grams positive isolates was (66.8%), whereas Grams negative isolates was (80.5%) with the overall MDR rate of (74.2%). The higher rate of MDR isolates among Grams negatives might be related to frequencies of infections caused by Grams-negative bacteria which leads them for frequent exposure to antimicrobial agents, which again helps them for selective pressure. In addition, significant resistance rates was observed against ampicillin, amoxicillin, ceftriaxone, co-trimoxazole and tetracycline with a pooled resistance ranges of (40.6–55.3%) in Grams positive and (52.8–85.7%) in Gram negative isolates. In contrast, slightly lower levels of resistance were observed against ciprofloxacin and gentamycin with a pooled resistance ranges of (23.8–32.4%) in Gram positive and (22.4–44.2%) in Gram negatives, respectively. The high levels of

resistance rate against the above antibiotics were also reported from many countries [38, 42, 47, 49, 52].

The root causes of the spread of antibiotic resistance are multi-factorial and interconnected. In the fact that, microorganisms have their own natural mechanisms for the development of resistance, however, many possible human related factors may contribute for highly aggravated and continuous deployment of resistance [53, 54]. Some of these factors may include inappropriate prescription practices, inadequate patient education, limited diagnostic facilities, unauthorized sale of antimicrobials, lack of appropriate functioning drug regulatory mechanisms, and non-human use of antimicrobials such as in animal production are the main drivers of AMR in both humans and animals, combined by a low level of compliance of the patients [53–55].

Ecological studies have demonstrated almost linear relationships between antibiotic consumption and the prevalence of AMR [55, 56]. Broad-spectrum antibiotics increase the selective pressure of bacteria and stimulate

the emergence of multi-drug resistant pathogens. A Survey study in Mongolia showed that, 42.3% of caregivers had used non prescribed antibiotics to treat symptoms in their child during the previous six months [57]. A systematic review and meta-analysis across 38 studies from 24 countries from eastern European and central Asian found that the pooled proportion of non-prescription supply of antibiotics was 62% [58]. Especially it is a common practice in developing countries, where the prevalence of infectious disease burden is aggravated by uncontrolled access to antibiotics. In those countries, antibiotics are prescribed to 44–97% of patients in hospital, and are often unnecessary [59–63].

In addition, although many countries have been endorsed clinical guidelines or treatment protocols for some common infections in hospitals, only 30% of health workers suggested that were generally accepted and followed that guidelines “all of the time” and 54% accepted and followed “sometimes” and around 15% used rarely [64]. This will lead to the increase of microbial resistance, an undesirable effect that causes antibiotic ineffectiveness and not only harmful to the patient but also to the society [63, 64]. With the new and emergent issue regarding the development of AMR, government agencies have engaged in new action plans in order to combat the AMR issue. However, actions toward this have been severely lacking in developing countries especially those in Africa where high quality regulatory agencies are lacking.

The current study had some limitations. First, although we have performed a comprehensive literature search, data from several provinces were limited, therefore the same estimates cannot be guaranteed from further studies that include these regions in the future. Second, we could not perform a detailed sub-group analysis other than what was presented in the manuscript, because the majority of studies included in the meta-analysis did not classify the neonatal sepsis cases based on type of delivery, birth weight and community-onset/hospital-associated infections.

Conclusions

Like other developing countries, the problems related to bloodstream infection that caused by microorganisms, including multi-drug resistance bacteria was significant in Ethiopia. The limited availability of data on culture confirmed bloodstream infections and underlying risk factors, and patterns of antimicrobial resistance may overshadow the problem. In addition, most etiological data

was from hospital-based studies and may have little relevance to community-acquired infections. Therefore, improving the knowledge of pathogens causing bloodstream infections with their antimicrobial resistance pattern is essential for devising management strategies.

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