

# Antimicrobial Resistance of Pseudomonas Aeruginosa Isolated From Patients With Wound Infection in Ethiopia. A Systematic Review Article

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## Research

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## Abstract

**Background:** Infectious diseases have been major cause of morbidity and mortality all over the globe. The ability of bacterial pathogens to adapt and overcoming to treat by different antibiotics has been challenging in patient management. The antimicrobial resistance rates of *Pseudomonas aeruginosa* are known to fluctuate extensively in different settings. Active inspection of trends in antibiotic resistance of *Pseudomonas aeruginosa* is essential for the selection of suitable antimicrobial agent for empirical therapy. The objective of our systematic review was to determine the national antimicrobial resistance profile of *Pseudomonas aeruginosa* isolated from patients with wound infection in Ethiopia.

**Methods:** We searched the Pub Med database in July and August 2018. We used the term 'antimicrobial resistance, *Pseudomonas aeruginosa*, wound and Ethiopia' to find articles published from 2011 to 2018 September. Only articles in English language were included. Full-text articles were incorporated if they reported the percentage of antibiotic resistance among clinical isolates of pathogenic bacteria collected from patients in any of the regions of Ethiopia. For overlapping studies reporting on the same clinical isolates, same study period and place, only the study with the largest sample size was included.

**Results:** From the 173 *Pseudomonas aeruginosa* isolates 99.5%, 95% of the isolates were resistant to ampicillin and Amoxicillin Clavulanic Acid respectively. From the isolates 28.8%, 29.7% and 39.6% of them were resistant to Gentamicine, ciprofloxacin and Ceftazidime respectively. Most of the isolates have limited susceptibility to ampicillin, Amoxicillin Clavulanic Acid, tetracycline, cotromoxazole, chloramphenicol and ceftriaxone.

**Conclusion:** Antimicrobial resistance is likely to become a challenge in Ethiopia and may be exacerbated by overuse of antibiotics, the lack of oversight of antibiotic prescription, and the lack of relevant local data on antimicrobial resistance. Therefore, existing antimicrobial stewardship programmes should be strengthened or, where they are not yet in place, they should be developed and implemented in all regional referral hospitals in response to these challenges and Health research institutes. Antimicrobial surveillance also needs to be strengthened.

## 1. Background:

Infectious diseases have been major cause of morbidity and mortality all over the globe. The ability of bacterial pathogens to adapt and to overcome the antibiotic treatment has been challenging. We are now faced with a growing population of antibiotic resistant bacteria that threaten the effective patient management especially for patients with surgical site infections [1].

Surgical site infection (SSI) is defined as a proliferation of pathogenic microorganisms which develops in an incision site either within the skin and subcutaneous fat (superficial) and musculofascial layers (deep) in an organ or cavity, if opened during surgery [2].

Hospital acquired surgical site infections (HAIs) are one of the major health problems throughout the globe and are a serious complication affecting patients [3, 4]. Pathogens that are capable of surviving in the hospital environment for extended period and resist against disinfection are mainly more important for HAIs [3]. SSIs account for a high proportion of the total amount of HAIs and have an enormous impact on patients health care expenditure, morbidity, and mortality universally [4, 5]. SSIs account for 20–25% of all hospital acquired infections globally [6]. Globally, surgical site infection rates have been reported to range from 2.5–41.9% [6]. The possibility of acquiring hospital infection on hospitalized patients in relation to operation is high, since about 77% of death of patients with hospital acquired infections was reported to be associated with postoperative infections [4]. The rate of HAIs is noticeably higher in several developing countries [3, 4]. The amount of surgical patients in developing countries is also rising but surgical care given to the patients is deprived [4].

The majorities of post-operative wound infections are hospital acquired, and fluctuate from one hospital to the other and are associated with complications, increased morbidity and mortality [7, 8]. The emergence of bacterial antimicrobial resistance has made the selection of empirical treatment more complicated and costly [9]. Wound infections by resistant bacteria have further deteriorated the condition in this regard [10]. Fast spread of resistant microorganisms affected the effectiveness of antimicrobials and created world-wide crisis [11]. The situation is serious in developing countries owing to unreasonable prescriptions of antimicrobial agents [12].

Infection in wound constitutes a major obstacle to healing and can have an adverse impact on the patient's quality of life as well as on the healing rate of the wound. Infected wounds are probably to be more painful, oversensitive and odorous, resulting in increased discomfort and inconvenience for the patient [13].

The common organisms that have been associated with wound infection consist of *Staphylococcus aureus* (*S. aureus*) which from a variety of studies have been found to account for 20–40% and *Pseudomonas aeruginosa* (*P. aeruginosa*) 5–15% of the nosocomial infection, with

infection mainly following surgery and burns. Other pathogens such as Enterococci and members of the Enterobacteriaceae have been implicated, mainly in immune compromised patients and following abdominal surgery [14].

*P.aeruginosa* is one of the opportunistic nosocomial pathogens, which causes a wide spectrum of infections and leads to significant morbidity especially in immune compromised patients. Due to its high drug resistance nature to many antibacterial agents, the mortality rate is extensive [15, 16]. Specific treatment options to patients with post surgical wound infections are mainly dependent on recent data from antimicrobial susceptibility test results generated by clinical laboratories or properly surveyed epidemiological information collected from ongoing nosocomial infection surveillance [17]. However, recently updated summarized data on isolated *P.aeruginosa* from hospitalized patients and their antimicrobial susceptibility status to guide post operative wound infection in the country is scarce. Understanding the current levels of antimicrobial resistance throughout the country could improve clinical practice by guiding empirical antibiotic choice [18]. To overcome this challenge, we reviewed the available evidences reported on the burden of antimicrobial resistance among *P.aeruginosa* isolates from wound infection in Ethiopia in order to inform current clinical practice and future research interventions to address antibiotic resistance.

Thus, this systematic review aimed at determining the current antimicrobial resistance profile of *Pseudomonas aeruginosa* isolated from patients with wound infection in Ethiopia.

## 1.1. Antimicrobial resistance patterns in wound isolates, especially *P.aeruginosa*

*Pseudomonas aeruginosa* is one of the most common gram negative bacterial pathogens associated with nosocomial infections [19, 20]. In addition to this, it is also widely spread in community acquired infections. Resistance to different anti-Pseudomonal agents is increasing from time to time, which challenges the choice of suitable treatment. The carbapenems are commonly considered as the most reliable agents for treating *P. aeruginosa* infections. The appearance of multidrug resistant *P. aeruginosa* remains concern of public health practitioners globally [20, 23]. Patients with *P. aeruginosa* wound infections have greater need for debridement and they frequently require re-grafting due to loss of skin grafts or allograft [21]. Skin and soft tissue infections caused by *P. aeruginosa* are also associated with prolonged hospital stay and increased mortality [22]. The mortality and morbidity associated with *P. aeruginosa* are mostly endorsed to insufficient empirical therapy and/ or delay in the beginning of appropriate therapy [19, 20].

Emergence of multi-drug resistance in *P. aeruginosa* is being reported globally, due to the blanket use of antibiotics [24]. The raise in occurrence of multidrug resistant strains is caused by a permanent selective pressure of frequently used antibiotics. This selective antibiotic pressure leads to expansion of bacterial resistance by favoring quick evolution of the bacterial genome [25]. Treatment of infections caused by this pathogen is becoming complicated, because of the increased rate of drug resistance. Knowledge on the resistance pattern of the local microbial flora is necessary for choice of appropriate antibiotic therapy. In this study, increased resistance to gentamicin, ciprofloxacin, ceftazidime, cefoperazone-sulbactam and meropenem was observed among the in-patients during the first study period. Several studies have reported such high rates of antibiotic resistance in *P. aeruginosa* isolated from hospitalized patients [26–28].

According to a study conducted on Antimicrobial Susceptibility Patterns of the Bacterial Isolates in Post-Operative Wound Infections in a Tertiary Care Hospital, Kathmandu, Nepal, 100% of the *Pseudomonas aeruginosa* isolates were resistant to Cephalexin and Cotrimoxazole. The resistance status for Ceftriaxone and Ciprofloxacin were 50%. In this study all the *Pseudomonas aeruginosa* isolates were 100% sensitive to Amikacin, Gentamicin, Norfloxacin and Ofloxacin [29].

Clinico-microbiological study of *Pseudomonas aeruginosa* in wound infections and the detection of metallo- $\beta$ -lactamase production conducted in India indicate that out of the 224 *Pseudomonas aeruginosa* isolates 38% showed resistance to gentamicin followed by ceftazidime (31.69%) and meropenem (33.03). In this report of the isolates, 100% were susceptible to polymyxin B and colistin, 92.8% were sensitive to imipenem [30].

A study on Antibiotics Susceptibility Pattern of *Pseudomonas aeruginosa* Isolated from Wounds in Patients Attending Ahmadu Bello University Teaching Hospital, Zaria, Nigeria indicates that strong resistance to cotrimoxazole (90.9%), amoxicillin (90.9%), tetracycline (81.8%) and augmentin (81.8%) [31].

Another study in the same country also shows that, resistance to different antibiotics against *P. aeruginosa* isolated from various samples was Ceftazidime (100%), Piperacillin-Tazobactam (99%), Amoxicillin Clavulanic Acid (91%), Amikacin (82%) and Ciprofloxacin (70%). In this study, over 65% of isolates were sensitive to Imipenem and 35% showed resistance to imipenem [32].

In Ethiopia a study conducted Prevalence of Multidrug Resistant Bacteria in Postoperative Wound Infections at Tikur Anbessa Specialized Hospital; Addis Ababa, Ethiopia of the 8 *Pseudomonas aeruginosa* isolated the resistance pattern were amoxicillin (100%), Amoxicillin-Clavulanic Acid and Sulphamethoxazole-Trimethoprim (87.5%) [32].

The antimicrobial resistance rates of *P. aeruginosa* are known to fluctuate extensively in different settings and period. Active inspection of trends in antibiotic resistance of *P. aeruginosa* is essential for the selection of suitable antimicrobial agent for empirical therapy. The objectives of this review were to assess the rates of antibiotic resistance and multidrug resistance among *P. aeruginosa* isolates from patients with wound infection.

## 2. Methods

### 2.1. Literature review

We searched the Pub Med database in July and August 2018. We used the term 'antimicrobial resistance, *Pseudomonas aeruginosa*, wound and Ethiopia' to find articles published from 2011 to 2018 September. Only articles in English language were included.

### 2.3. Study selection criteria

Full-text articles were incorporated if they reported the percentage of antibiotic resistance among clinical isolates of pathogenic bacteria collected from patients in any of the regions of Ethiopia. Eligible studies were essential to describe the patient population studied, organism isolated, definite laboratory methods used for the determination of pathogen antimicrobial sensitivity patterns, and an interpretation of the specific minimum inhibitory concentration breakpoints or the diameter of the zone of inhibition of the antibiotics tested as described by the Clinical and Laboratory Standards Institute [38]. For overlapping studies reporting on the same clinical isolates, same study period and place, only the study with the largest sample size was included. In an effort to incorporate contemporary, relevant antimicrobial resistance data, only studies published from 2011 onwards were included in the review.

### 2.4. Data extraction

The extracted data included *Pseudomonas aeruginosa* isolated, the number of isolates tested for Antimicrobial resistance, specific antibiotics tested for resistance, and percentage of the isolate resistant to each antibiotic.

## 3. Results

We initially identified 20 articles: of the 20 article 2 of them were repeated in the same year and place, 3 of them were not only from post operative isolates, and 3 of them were not clear with the antimicrobial resistance pattern presented. Therefore, 10 of the 20 articles were excluded. The remaining 10 articles were included in this review, two describing antimicrobial resistance patterns in Gondar [31, 40], three in Jimma [32, 33, 36], one in Hawassa [34], one in Mekelle[35], one in Bahrdar[39] and two in Addis Ababa. [30, 37] (Table 1). Neither studies from other regions met inclusion criteria for this review. All studies were hospital-based and cross-sectional in design, and the majority described both community- and hospital-acquired infections.

Table 1  
Antimicrobial Resistance profile of *Pseudomonas aeruginosa* isolated from patients with wound infection in Ethiopia

Bacterial isolate	No of species	Antimicrobial resistance pattern										Study area	Reference	Study Period
		AMP	C	TE	SXT	CN	CIP	CRO	AMC	CAZ	CTX			
<i>Paeruginosa</i>	3	100	100	100	100	66.7	33.3	100	-	-	-	Gondar	31	2011
	74	97.3	74.3		88	10.8	-	9.5	-	-	12.2	Jimma	32	2013
	11	100	82	82	73	18	0	63.6	-	-	-	Jimma	33	2014
	18	100	100		66.7	50	0	100	100	-	-	Hawasa	34	2014
	11	100	-	100	-	0	81.8	100	100	-	-	Mekelle	35	2014
	8	-	-	-	-	50	50	-	87.5	-	-	Jimma	36	2016
	6	100	50	50	-	0	33.3	83.3	100	33.3	100	Addis Ababa	37	2016
	26	-	-	-	33.3	30.4	19.2	-	-	73.1	-	Bahrdar	39	2016
	8		37.5	100	87.5	25	12.7		87.5	12.5		Addis Ababa	30	2017
8	-	75	-	-	37.5	37.5	37.5				Gondar	40	2017	
Over all %	173	99.5	74	86.4	74.7	28.8	29.7	70.5	95	39.6	56			
<b>AMP:</b> ampicillin; <b>CRO:</b> ceftriaxon; <b>CIP:</b> ciprofloxacin; <b>SXT:</b> co-trimoxazole;; <b>TE:</b> tetracycline, <b>CN:</b> Gentamicin, <b>CAZ:</b> Ceftazidime, <b>AK:</b> Amikacin, <b>AMC:</b> Amoxicillin Clavulanic Acid, <b>C =</b> chloramphenicol; <b>CTX =</b> Cefotaxim														

As we can see from this review of the 173 *Pseudomonas aeruginosa* isolates 99.5%, 95% of the isolates were resistant to ampicillin and amoxicillin clavulanic acid respectively. From the isolates 28.8%, 29.7% and 39.6% of them were resistant to gentamicine, ciprofloxacin and ceftazidime respectively. Even though antimicrobial resistance varies from place to place, according to the findings we found most of the *Pseudomonas aeruginosa* isolates have limited susceptibility to ampicillin, Amoxicillin Clavulanic Acid, tetracycline, cotrimoxazole, chloramphenicol and ceftriaxone, though based on the CLSI guideline these antibiotics are not recommended to be tested for *Pseudomonas aeruginosa* isolates due to intrinsic resistance behavior, but in most of the journals these antibiotics were tested their susceptibility status to the isolate.

## Discussion

In this review, we summarize the findings of 10 studies that demonstrate significant resistance in Ethiopia to antibiotics important for everyday use. Although antimicrobial resistance varies in different regions of the country, according to the findings we found most of the *Pseudomonas aeruginosa* isolates have limited susceptibility to ampicillin, Amoxicillin Clavulanic Acid, tetracycline, cotrimoxazole, chloramphenicol and ceftriaxone, though based on the CLSI guideline these antibiotics are not recommended to be tested for *Pseudomonas aeruginosa* isolates due to intrinsic resistance behavior, but in most of the journals these antibiotics were tested their susceptibility status to the isolate.

Several published papers we reviewed reports that this isolate was resistant to multiple antibiotics. Antibiotic resistance to multiple drugs was most common from the organisms isolated from hospital-acquired infections in post-operative patients and hospitalized adults [31, 35]. However, the susceptibility of the organisms to gentamicine and ciprofloxacin was relatively reported to be good; thus, these antibiotics may be the drug of choice for empirical use against post-operative nosocomial infections with *Pseudomonas aeruginosa*. The finding of multi-drug resistance in this population suggests that efforts to encourage appropriate antibiotic use and microbiological sampling of infected patients should be targeted to these groups in low-resource settings.

The evidence presented in this review indicates that antimicrobial resistance, especially to the widely-used antibiotics (ampicillin, tetracyclines and cotrimoxazole, ceftriaxone and Amoxicillin Clavulanic Acid), is prevalent and common in Ethiopia and may be a growing problem, especially among hospitalized. However, resistance is likely under-reported in our country as noted by the WHO Global Report on antimicrobial resistance in 2014, due to limited availability of diagnostic testing, microbiology support and limited comparability of laboratory standards. Many of the same factors leading to the inability to test clinical isolates for antimicrobial susceptibility contribute to antibiotic overuse and misuse when laboratory data are lacking and can contribute to exacerbation of antimicrobial resistance.

Even when information concerning antimicrobial resistance is available, it may not be appropriately communicated to those prescribing medications in the country, due to inadequate regional laboratory strategic plans throughout the country. In addition, guidelines regarding appropriate selection of drugs are not strictly followed or inadequate. Reasons for these problems are a lack of rigorous infection control procedures, all of which could lead to the development and increase in antibiotic resistant bacteria. These factors combine to support the spread of existing antimicrobial resistance throughout Ethiopia.

## 4. Conclusion

Based on the findings in this review, resistance to commonly-used antibiotics is common in Ethiopia. Multi-drug resistance has been distinguished as an increasing warning in the country and threatens to additionally complicate the drug resistance burden. Information from interventional studies planned to reduce antimicrobial resistance are mainly lacking in the Ethiopian context, where infectious disease prevalence is high. The lack of concrete data on hospital-acquired infections and status of antimicrobial resistance in low-income countries calls for vigorous investigation and surveillance to better define the problem. There is a need for countries to promote acceptance of antimicrobial stewardship as a programmatic strategy, including pharmacy management, laboratory quality control, complete microbiology investigations and creation and dissemination of regional standard antibiograms.

Antimicrobial resistance is likely to become an even greater problem in Ethiopia and may be exacerbated by overuse of antibiotics, the lack of oversight of antibiotic prescription, and the paucity of relevant local data on antimicrobial resistance. To address these issues, existing antimicrobial stewardship programmes should be strengthened or, where they are not yet in place, they should be developed and implemented in all regional referral hospitals in response to these challenges and Health research institutes. Antimicrobial surveillance also needs to be strengthened.

## Abbreviations

AMR: Antimicrobial resistance, SSI: Surgical site infection, WHO: World health organization, CLSI: Clinical and laboratory standards institute, HAI: Hospital acquired infection

## Declarations

### Abbreviations:

AMR: Antimicrobial resistance, SSI: Surgical site infection, WHO: World health organization, CLSI: Clinical and laboratory standards institute, HAI: Hospital acquired infection

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### Authors' contributions

This work was carried out in collaboration between all authors. G.G. was the project leader. G.G, G.T. and A.G. performed the literature search, data analysis, and wrote the first draft of the manuscript and managed manuscript revisions. A.A. participated in data analysis and manuscript writing and revisions. All authors read and approved the final manuscript.

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### Availability of data and materials

The data that support the findings of this review are available even on line in pubmed and other databases

### Ethics approval and consent to participate

Not applicable

## Consent for publication

Not applicable.

## Competing Interests

All authors declare that they have no conflict of interests associated with the publication of this review.

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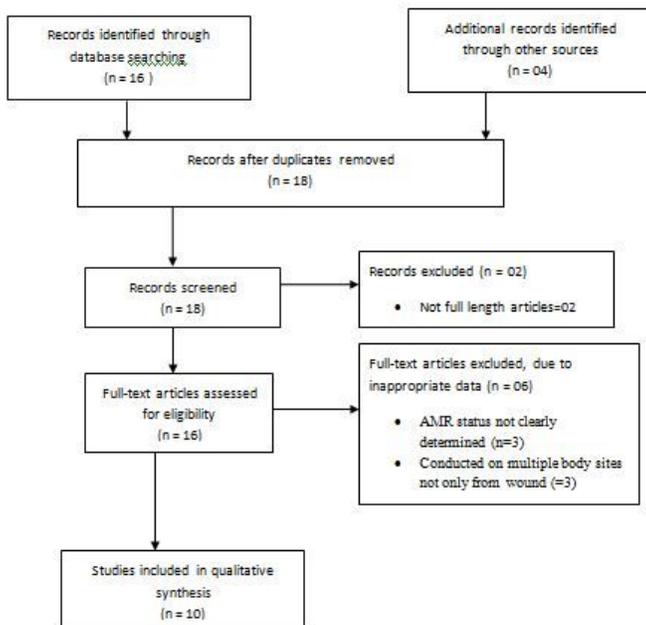
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## Figures



**Figure 1**

Selection of publications for inclusion in this review.