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Empirical antibiotherapy as a potential driver of antibiotic resistance: observations from a point prevalence survey of antibiotic consumption and resistance in Gombe, Nigeria

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Abstract:

Background: Empirical use of antibiotics is a standard practice in the treatment of infections worldwide. However, its over utilization without subsequent culture and antibiotic susceptibility testing could be a major driver of resistance. Over reliance on empirical antibiotherapy is common in most developing countries where antibiotic policies and availability or utilization of clinical microbiology laboratory are suboptimal. A standardized approach to point prevalence survey (PPS) on antimicrobial use (AMU) in hospitals was employed to assess the antimicrobial prescribing practices in Federal Teaching Hospital Gombe (FTHG), Nigeria.
Methodology: A PPS was conducted in April 2019 at FTHG by recruiting all in-patients present in the hospital on the day of survey. Data obtained from patients' records included details of the type and indication for antibiotherapy. A customized online application developed by the University of Antwerp (www.global-pps.be) was used for data-entry, validation, analysis and reporting.
Results: Of the total 326 patients who were on admission on the day of survey, 70.6% and 73.4% were on at least one antibiotic in adult and paediatric wards respectively. Most commonly used antibiotics include beta lactams such as cephalosporins (29.2%) and penicillins (22.8%), fluoroquinolones (12.4%), aminoglycosides (9.1%) and macrolides (3.4%). Among patients on antibiotics, route of administration was mainly parenteral (71.6%) while 44.8% were on more than one antibiotic. Overall, 91.3% of the antibiotic treatments were empirical with adults, children and neonates accounting for 96.4%, 77.6% and 100.0% respectively. Empirical antibiotic use is also high in medical wards (86.3%), surgical wards (89.9%) and intensive care unit (100.0%).
Conclusion: There is predominance and over-reliance on empirical antibiotherapy in our hospital. It further exposes the poor utilization of clinical microbiology laboratory and the potential for development of antibiotic resistance with resultant increase in morbidity/mortality and poor patient safety. There is need for further studies to highlight the dangers of over-reliance on empirical antibiotherapy and herald improvement in development and implementation of antibiotic stewardship programme.

Keywords: Empirical antibiotherapy, antimicrobial resistance, point prevalence survey, antimicrobial stewardship

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L'antibiothérapie empirique comme moteur potentiel de la résistance aux antibiotiques: observations d'une enquête ponctuelle de prévalence de la consommation et de la résistance aux antibiotiques à Gombe, au Nigéria

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Abstrait:

Contexte: L'utilisation empirique d'antibiotiques est une pratique courante dans le traitement des infections dans le monde entier. Cependant, sa surutilisation sans culture ultérieure ni test de sensibilité aux antibiotiques pourrait être un facteur majeur de résistance. Le recours excessif à l'antibiothérapie empirique est courant dans la plupart des pays en développement où les politiques d'antibiotiques et la disponibilité ou l'utilisation du laboratoire de microbiologie clinique sont sous-optimales. Une approche standardisée de l'enquête de prévalence ponctuelle (PPS) sur l'utilisation des antimicrobiens (AMU) dans les hôpitaux a été utilisée pour évaluer les pratiques de prescription d'antimicrobiens au Federal Teaching Hospital Gombe (FTHG), au Nigéria.
Méthodologie: Un PPS a été réalisé en avril 2019 au FTHG en recrutant tous les patients hospitalisés présents à l'hôpital le jour de l'enquête. Les données obtenues à partir des dossiers des patients comprenaient des détails sur le type et l'indication de l'antibiothérapie. Une application en ligne personnalisée développée par l'Université d'Anvers (www.global-pps.be) a été utilisée pour la saisie, la validation, l'analyse et le reporting des données.
Résultats: Sur les 326 patients au total qui étaient admis le jour de l'enquête, 70,6% et 73,4% prenaient au moins un antibiotique dans les services pour adultes et pédiatriques respectivement. Les antibiotiques les plus couramment utilisés comprennent les bêta-lactamines telles que les céphalosporines (29,2%) et les pénicillines (22,8%), les fluoroquinolones (12,4%), les aminosides (9,1%) et les macrolides (3,4%). Parmi les patients' sous antibiotiques, la voie d'administration était principalement parentérale (71,6%) tandis que 44,8% prenaient plus d'un antibiotique. Dans l'ensemble, 91,3% des traitements antibiotiques étaient empiriques, les adultes, les enfants et les nouveau-nés représentant respectivement 96,4%, 77,6% et 100,0%. L'utilisation empirique d'antibiotiques est également élevée dans les services médicaux (86,3%), les services chirurgicaux (89,9%) et les unités de soins intensifs (100,0%).
Conclusion: Il y a une prédominance et une dépendance excessive à l'antibiothérapie empirique dans notre hôpital. Il expose en outre la mauvaise utilisation du laboratoire de microbiologie clinique et le potentiel de développement d'une résistance aux antibiotiques avec une augmentation résultante de la morbidité/mortalité et une mauvaise sécurité des patients. Des études supplémentaires sont nécessaires pour mettre en évidence les dangers d'une dépendance excessive à l'antibiothérapie empirique et annoncer une amélioration dans le développement et la mise en œuvre d'un programme de gestion des antibiotiques.

Mots clés: antibiothérapie empirique, résistance aux antimicrobiens, enquête ponctuelle de prévalence, gestion des antimicrobiens

Introduction:

Antimicrobials which include antibiotics, antivirals, antifungals and antiparasitics are drugs used to prevent and treat infections in humans, animals and plants while antimicrobial resistance (AMR) occurs when bacteria, viruses, fungi and parasites change over time and no longer respond to previous medications thereby making them more difficult to treat, with resultant increase in risk of spread, morbidity and mortality (1). Multidrug resistant micro-organisms (MDROs) have remained one of the greatest challenges to patient safety affecting all facets of infection prevention and control (IPC), with poor patient outcome, increased cost of care and varying effects among different countries worldwide (1-4). The World Health Organization (WHO) declared AMR as one of the top ten (10) global public health threats facing humanity and mainly driven by misuse and overuse of antimicrobials with worsening effects in developing countries (1,5).

Inadequate and unnecessarily broad-spectrum empiric antibiotic therapy has been linked to poor patient outcome largely due to AMR (6,7). Although universally practiced, empirical antibiotherapy is among the most common drivers of AMR through the overuse of antibiotics with many MDROs being allowed to flourish through initial treatment with ineffective medications (6). The variations between empirical coverage and subsequent detection of MDROs is not an uncommon observation even in advanced countries (8). A study revealed a discordant empirical antibiotic therapy approximately 20% among patients with bloodstream infections in US hospitals which was closely associated with

infections with MDROs (7). This buttresses the need for timely isolation and identification of the correct pathogen, which is very critical in the management of infectious diseases and in avoiding misuse and abuse of antibiotics (9).

There is a link between MDROs/AMR and healthcare associated infections (HAIs) with empiric use of antibiotics, and even in settings where antibiotic guidelines are available (10). The ability of healthcare providers to accurately match their antibiotic use with prevalent nosocomial pathogens in most hospitals remains low; hence the discouragement of over-reliance on empirical antibiotherapy without appropriate/ timely culture results.[8]

Several studies carried out in Nigeria explored antimicrobial prescribing patterns in hospitals and have revealed the need for harmonized approach to combat AMR through institutionalization of antimicrobial stewardship programmes (ASPs) and other necessary IPC and patient safety measures (11-13). AMR is a complex challenge that requires collective multisectoral approach with the "One Health" approach which brings together multiple sectors and stakeholders required for all programmes, policies, legislation and research being considered as the most viable approach to tackling the menace (1,2). Rational use of antibiotics through reasonable use of empirical antibiotherapy in hospitals and ensuring optimal utilization of laboratories is one easily implementable measure that can be applied in most Nigerian hospitals at a relatively low cost or extra burden on the system.

This study used the Global Point Prevalence Survey (G-PPS) platform developed by the University of Antwerp, to explore empirical antibiotherapy in FTHG as a potential driver of AMR and the risk of increased HAIs and a threat to patient safety.

Materials and method:

This was a cross sectional hospital-based PPS study conducted in April 2019 at the FTHG; a 500-bedded tertiary hospital in north-eastern Nigeria with institutionalized IPC and patient safety programmes. All in-patients who have been on admission at least 24 hours before the day of the survey and were present by 8am, were included in the study. Data obtained from patients' records included details of the type and indication for antibiotherapy. Anonymized patients' data for the study included an automatically generated unique survey number, age, gender, antimicrobial agents, number of doses per day, route of administration, indications for treatment and documentation of indication, stop or review date of prescription, microbiological data and compliance with prescribing guidelines. The survey for all patients in each particular ward was completed on a single day.

Data-entry, validation, analysis and reporting were done using the customized online application developed by the University of Antwerp (www.global-pps.be). Frequencies and proportions were used to present qualitative variables while Chi-square test was used to determine associations. P-value of <0.05 was set to determine statistically significant associations among the variables. Ethical approval for the study was obtained from the Research and Ethics Committee of FTHG.

Results:

Of the total 326 patients who were on admission on the day of survey, 70.6% and 73.4% were on at least one antibiotic in adult and paediatric wards respectively. Most commonly used antibiotics include beta lactams such as cephalosporins (29.2%) and penicillins (22. 8%), fluoroquinolones (12.4%), aminoglycosides (9.1%) and macrolides (3.4%). Among patients on antibiotics, route of administration was mainly parenteral (71.6%). Almost half (44.8%) of the patients were on more than one antibiotic. The pattern of empirical antibiotherapy as observed among different patient groups/wards and among HAIs and community acquired infections (CAIs) were as presented in Fig 1.

Quality indicators for antibiotic use in our hospital revealed documentation of indication for prescription in case notes for all the patients but variable rate in documentation of stop/review dates, with total absence of antibiotic guidelines, as highlighted in Table 1.

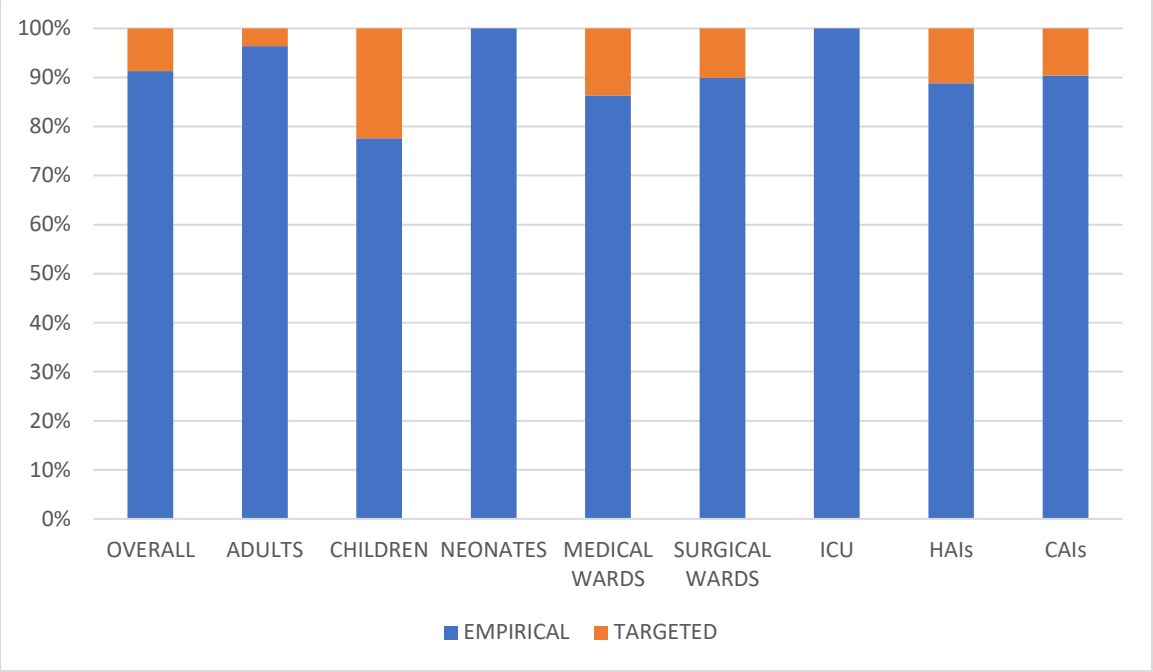

Fig 1: Rate of empirical and targeted antibiotherapy with respect to category of inpatients, ward and infection types

Table 1: Summary of some quality indicators for antibiotic use in Medical, Surgical and Intensive Care Unit

Quality indicator	Medical n (%)	Surgical n (%)	ICU n (%)
Reason in notes documented	81 (100)	184 (92.9)	19 (100)
Stop/review date documented	78 (96.3)	197 (99.5)	17 (89.5)
Guidelines absent	81 (100)	198 (100)	19 (100)

ICU = Intensive Care Unit; n = number of patients or cases

Discussion:

The overall rate of antibiotic prescription (>70%) in virtually all parts of the hospital observed in this study is not different from other reports on antimicrobial prescribing patterns and consumption in Nigeria (11-14). It is therefore obvious that majority of patients receives a minimum of one antimicrobial agent while on admission in Nigerian hospitals which is also a similar finding across other countries (15). Majority (>90%) of antibiotic therapy in our hospital were empirical and broad spectrum. This is higher than rates reported in studies from some parts of the world but reflects similar rates in other Nigerian studies (6,8,11-14).

Although the rate of inappropriate empirical antibiotic use could not be ascertained in this study, other reports have shown high rates that ranged between 14.1% to 78.9% (16,17). Approximately one in five patients with bloodstream infections in the US hospitals received discordant empirical antibiotic therapy with resultant rise in AMR (7). Inappropriate and discordant empirical antibiotic therapy has been shown to increase the 30-day and in-hospital mortality (7,16,17). Infection with antibiotic-resistant pathogens strongly predicted receiving discordant empirical therapy and therefore, misuse and overuse of broad-spectrum antibiotics prior to the availability of culture results may be counterproductive (7,18). It is therefore clear that empiric antibiotics may be irrelevant in many instances and should be cautiously handled (19). This re-emphasizes the need for institutionalization of ASPs for better patient safety and improved quality of care in all hospitals.

Appropriate selection of route of administration and switch from parenteral to oral antibiotics is one of the cardinal principles of antibiotherapy which may not be observed regularly as shown by high level (71.6%) of parenteral administration in our centre and

other local findings (9, 11-13). Most commonly used antibiotics in our hospital were beta lactams such as cephalosporins and penicillins, and the fluoroquinolones. This is similar to other findings from Nigeria, which could be due to similarities in training and approach to patient care without uniform/centre-based guidelines on antimicrobial prescribing (11-14). Findings from this study revealed that many (44.8%) patients were on more than one antibiotic which reflect the same pattern seen in many studies from Nigeria (11-14).

There was an observed excellent documentation of reasons for antibiotic prescription and variable documentation of the stop/review dates in this study, but there were absent antibiotic guidelines/compliance. This is similar to a recent report by Fowotade et al., (11) but different from the findings reported by Oduyebo et al., (13). Variations in the hospitals and differences in hospital policies and timing of the studies could explain the similarities and differences. This underscores the need for concerted efforts to have uniform antibiotic prescribing guidelines at both national and local levels in all hospitals in Nigeria, a task that the national antibiotic stewardship team, in collaboration with the G-PPS network, has started to establish to strengthen ASPs across the country.

Conclusion:

This PPS shows that majority of in-patients in FTHG are on empirical antibiotic therapy and on at least one antibiotic. Over-reliance on empirical antibiotherapy is potentially a major driver of AMR, which will worsen outcomes for both CAIs and HAIs. Strengthening of ASP is necessary for better patient safety in the hospital.

Conflict of interest:

Authors declare no conflict of interest.

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Previous publication:

Oral presentation of this paper was made at the Virtual Conference of the Clinical Microbiology and Infectious Disease Society of Nigeria (CLIMIDSON) via Zoom on 26th - 27th November 2020, and the abstract has been published in the conference programme.

References:

1. World Health Organization. Antimicrobial resistance 2020.https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance (last accessed 02/01/2021
2. Gil-Gil, T., Laborda, P., Sanz-García, F., Hernando-Amado, S., Blanco, P., and Martínez, J. L. Antimicrobial resistance: A multifaceted problem with multipronged solutions. Microbiology Open. 2019; 8 (11). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6855134/
3. Mathur, P., and Singh, S. Multidrug Resistance in Bacteria: A Serious Patient Safety Challenge for India. J Lab Physicians. 2013; 5 (1): 5–10.
4. Fauci, A. S., and Marston, H. D. The perpetual challenge of antimicrobial resistance. JAMA 2014; 311 (18): 1853-1854. http://dx.doi.org/10.1001/jama.2014.2465
5. Ayukekbong, J. A., Ntemgwa, M., and Atabe, A. N. The threat of antimicrobial resistance in developing countries: causes and control strategies. Antimicrob Resist Infect Control. 2017; 6 (1): 47.
6. Rhee, C., Kadri, S. S., Dekker, J. P., et al. Prevalence of Antibiotic-Resistant Pathogens in Culture-Proven Sepsis and Outcomes Associated with Inadequate and Broad-Spectrum Empiric Antibiotic Use. JAMA Netw Open.2020;3(4). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7163409/
7. Kadri, S. S., Lai, Y. L., Warner, S., et al. Inappropriate empirical antibiotic therapy for bloodstream infections based on discordant in-vitro susceptibilities: a retrospective cohort analysis of prevalence, predictors, and mortality risk in US hospitals. Lancet Infect Dis. 2020. doi:10.1016/s1473-3099(20)30477-1
8. Jones, B. E., Brown, K. A., Jones, M. M., et al. Variation in Empiric Coverage Versus Detection of Methicillin-Resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* in Hospitalizations for Community-Onset Pneumonia Across 128 US Veterans Affairs Medical Centers. Infect Control Hosp Epidemiol. 2017;38 (8): 937–944.
9. Leekha, S., Terrell, C. L., and Edson, R. S. General Principles of Antimicrobial Therapy. Mayo Clin Proc. 2011; 86 (2): 156–167.
10. Bostwick, A. D., Jones, B. E., Paine, R., Goetz, M. B., Samore, M., and Jones, M. Potential Impact of Hospital-acquired Pneumonia Guidelines on Empiric Antibiotics. An Evaluation of 113 Veterans Affairs Medical Centers. Ann Am Thorac Soc. 2019; 16 (11): 1392–1398.
11. Fowotade, A., Fasuyi, T., Aigbovo, O., et al. Point Prevalence Survey of Antimicrobial Prescribing in a Nigerian Hospital: Findings and Implications on Antimicrobial Resistance. West Afr J Med. 2020; 37 (3): 216–220.
12. Abubakar, U. Antibiotic use among hospitalized patients in northern Nigeria: a multicenter point-prevalence survey. BMC Infect Dis. 2020; 20. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6990515/
13. Oduyebo, O. O., Olayinka, A. T., Iregbu, K. C., et al. A point prevalence survey of antimicrobial prescribing in four Nigerian Tertiary Hospitals. Ann Trop Pathol. 2017; 8 (1): 42.
14. Umeokonkwo, C. D., Madubueze, U. C., Onah, C. K., et al. Point prevalence survey of antimicrobial prescription in a tertiary hospital in South East Nigeria: A call for improved antibiotic stewardship. J Glob Antimicrob Resist. 2019; 17: 291–295.
15. Versporten, A., Zarb, P., Caniaux, I., et al. Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. Lancet Glob Hlth. 2018; 6: e619-e629.
16. Marquet, K., Liesenborgs, A., Bergs, J., Vleugels, A., and Claes, N. Incidence and outcome of inappropriate in-hospital empiric antibiotics for severe infection: a systematic review and meta-analysis. Crit Care. 2015; 19 (1): 1–12.
17. Osih, R. B., McGregor, J. C., Rich, S. E., et al. Impact

of Empiric Antibiotic Therapy on Outcomes in Patients with *Pseudomonas aeruginosa* Bacteremia. Antimicrob Agents Chemother. 2007; 51 (3): 839–844.
18. Thom, K. A., Schweizer, M. L., Osih, R. B., et al. Impact of Empiric Antimicrobial Therapy on Outcomes in Patients with *Escherichia coli* and *Klebsiella pneumoniae* Bacteremia: A Cohort Study. BMC Infect Dis. 2008; 8 (1): 1–9.
19. Schuttevaer, R., Alsma, J., Brink, A., et al. Appropriate empirical antibiotic therapy and mortality: Conflicting data explained by residual confounding. PLoS One. 2019; 14 (11): e0225478.