Journal of
Antibiotics and Antimicrobial Agents

JScholar
Fostering Scholarly Communication

Research Article Open Access

Safety and Clinical Outcomes of Antibiotic De-escalation as Part of Antimicrobial Stewardship (AMS) Program: A Retrospective Observational Descriptive Study in an Intensive Care Unit

Ann Lisa Arulappen[1,2*], Monica Danial[3] and Cheng Joo Thye[4]

[1]Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, University Sains Malaysia, Georgetown, Malaysia
[2]Pharmacy Department, Hospital Seberang Jaya, Georgetown, Malaysia
[3]Clinical Research Center, Hospital Seberang Jaya, Georgetown, Malaysia
[4]Internal Medicine (General) | Infectious Diseases, Jalan Hospital Ipoh 30990 Perak Darul Ridzuan, Malaysia

***Corresponding authors:** Ann Lisa Arulappen, Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, University Sains Malaysia, Pharmacy Department, Hospital Seberang Jaya, Georgetown, Malaysia, Tel: +60175013340, E-mail: annlisaarul@yahoo.com

Received Date: November 05, 2021 **Accepted Date:** December 05, 2021 **Published Date:** December 07, 2021

Citation: Ann Lisa Arulappen (2021) Safety and Clinical Outcomes of Antibiotic De-escalation as Part of Antimicrobial Stewardship (AMS) Program: A Retrospective Observational Descriptive Study in an Intensive Care Unit. J Antibiot Antimicrob Agents 1: 1-9.

Abstract

Introduction: Antimicrobial resistance has been a global issue past many decades and mortality rate in regards to it is multiplying drastically every other day. De-escalation of antibiotic therapy is a measure to overcome this issue before it is too late. Having said this, many measures have been enforced by the Ministry of Health, Malaysia to actively cultivate the culture of antimicrobial stewardship including de-escalation of therapy among the clinicians.

Method: This was a retrospective study from October 2019 to October 2020 involving patients aged 18 years and above admitted to the intensive care unit for ventilator support and started on broader spectrum of antibiotics subsequently de-escalated to narrower spectrum of antibiotics upon 72 hours review by the AMS team. The multiple outcomes measured in this study are sepsis free after treatment, the survival upon discharge, readmission within 30 days and also cost savings associated with the antibiotics only.

Results: A total of 32 patients were recruited and eligible to be part of this study. Among the 32 patients, 29 (90.6%) of them presented with sepsis upon admission whereas 3 (9.4%) patients were sepsis free. Nevertheless, about 21 (65.6%) patients were sepsis free after being treated in ICU and remaining 11 (34.4%) were still treated as sepsis. Majority of the study population survived upon discharge precisely 22 patients (68.8%). All 22 patients had no history of readmission within 30 days after being discharge. Only 1 patient died additionally post 30 days from the date of discharge accumulating the total number of fatalities up to 11 (34.4%). The total cost savings was approximately 52.7% which is equivalent to MYR 5,174.47.

Conclusion: It can be concluded that de-escalation of antibiotics therapy is not associated with increased risk of mortality despite no positive culture even in critically ill patients.

Keywords: Antimicrobial Stewardship; De-escalation; Critically ill

Introduction

Antimicrobial resistance is a threat globally which refers to resistance of a microorganism to the antimicrobials that were initially efficacious in eradicating the infections in regards to the injudicious use. The emergence of antimicrobial resistance perhaps cause resistance to the first line antimicrobials thereby requires to use the second or third line antimicrobials which possibly less effective, more toxic and more costly. The pace of antimicrobials development has slowed remarkably past these few decades [1-3]. As more resistance is acquired, there will be no effective antimicrobials left behind. Antimicrobial resistance impacts negatively in terms of patient outcomes, poses a major threat for the patient safety, increases health expenditure and consequently led to no treatment options left even for common infections.

Therefore, antimicrobial stewardship program have been developed to improve and promote the judicious use of antimicrobials through optimal antimicrobial selection; right choice of antimicrobial, right route of administration, right dose, right time, right duration and minimize harm to the patients. Enforcement of antimicrobial stewardship program have a significant impact on the healthcare system including cost savings, improvisation of antibiogram and reduce the prevalence of resistant organisms [4, 5].

The antimicrobial stewardship program consists of various activities or initiatives including antimicrobial streamlining. One of the principles of streamlining is de-escalation of therapy means switching from a broader spectrum of antimicrobial to a narrower spectrum. The use of broad spectrum antimicrobial empirically may exacerbate the risk of antimicrobial resistance. The de-escalation strategy has the potential to improve patient outcomes without compromising patient safety.

However, de-escalation of therapy is not made widely and confidently by the medical practitioners in view of the stigma that such approach may jeopardize the patients' quality of life despite there are many studies have proved that de-escalation of therapy upon review was not associated with increased mortality rates [6-8]. A random survey conducted among the local medical practitioners in this study setting confessed that only 2 out 26 of them approximately 92% would actively de-escalate the antimicrobial therapy if patient's condition allows to do so. Thus, this study was conducted with the aim to correlate the consequences of active de-escalation of antimicrobial therapy and the associated mortality risk. The outcome of this study was expected to serve as a platform which enables the medical practitioners to confidently proceed with the de-escalation of therapy accordingly as this study involves local population.

Methods

Study Location

This single center study was carried out in an Intensive Care Unit with 17- bed occupancy capacity lead by Anesthetists. Also, there are two in-house Infectious Diseases Consultants and has led the Antimicrobial Stewardship (AMS) team in this facility. Ethical board approval by Medical Research and Ethics Committee (MREC) was obtained prior to the initiation of this study.

Data Collection

The data pertaining to this de-escalation of antimicrobial study was obtained retrospectively. The study period took place approximately a year from October 2019 to October 2020 involving patients aged 18 years and above admitted to the intensive care unit for ventilator support and started on broader spectrum of antibiotics subsequently de-escalated to narrower spectrum of antibiotics upon 72 hours review by the AMS team. However, those patients with life expectancy lesser than 24 hours were excluded from this study. The data was conveyed to an Excel worksheet using coding system. The data collected includes patient demographics, previous and current antibiotics history, presence of comorbidities, types of infections treated, sites of infections involved, pre and post de-escalation of therapy associated vital signs and lab parameters, and additionally the length of stay at both intensive care unit and hospital. The required information is obtained from the patients' record files.

Outcome measurement

There are multiple outcomes being measured in this study. Firstly, the sepsis free after treatment was determined once the patient completes the antibiotic course and there is no sign of bacteremia thereafter based on the repeated culture results.

Secondly, the survival upon discharge was analyzed after the patient is certified to be sent home by the medical practitioners rather than including those patients discharged at own risk.

Thirdly, readmission within 30 days was evaluated upon those patients whom have been discharged after being sepsis free and were readmitted again within 30 days from the last date of discharge from the facility.

Fourthly, the mortality post 30 days was weighed after 30 days from the date of discharge. All the four types of outcomes mentioned above would be a direct yes or no statement indeed.

Lastly, cost savings was also computed in this study. The cost savings calculated in this study was solely based on the antibiotic usage. It excludes the other hospital charges including room bills, ventilator charges and consultation fees. The cost savings was reported in Ringgit Malaysia (MYR).

Statistical Analysis

Descriptive statistical analysis has performed using SPSS. The data during pre and post de-escalation periods were related using paired t-test and Pearson's chi-square test whereas the association between presence of comorbidities and certain parameters of the patients were determined by latter test. A p-value of < 0.05 was considered significant.

Results

Throughout one year of the study period, a total 1,270 patients were admitted to the intensive care unit for ventilator support and approximately 1,016 patients were started on antibiotics. About 406 patients were given broad spectrum antibiotics including Cefepime, Piperacillin-tazobactam, Meropenem. Meanwhile, out of this 406 patients, 98 patients were given antibiotics as for targeted treatment whereas the remaining was purely empirical. Approximately 59 patients from remaining 308 were referred to AMS team for expert opinion. Only 32 patients consist of 20 males (62.5%) and 12 females (37.5%) met the inclusion criteria consequently recruited in this study. The demographics characteristics of the patients are tabulated in Table 1. From the 32 patients, 21 (65.6%) of them were treated as nosocomial pneumonia including hospital acquired pneumonia (HAP) and ventilator acquired pneumonia (VAP), 7 (21.9%) patients were treated as complicated intra-abdominal infection (cIAI) and remaining 4 (12.5%) patients were treated as complicated skin or soft tissue infection (cSSI). In terms of ventilator settings, 13 patients were given Bi-level ventilation with FiO_2 ranging from 0.4-0.7, another 17 patients were given Continuous Positive Airway Pressure (CPAP) ventilation with FiO_2 ranging from 0.4-0.5 and remaining 2 patients were given high flow nasal prong therapy up to 6L (NPO_2).

Table 1: Demographic characteristics of patients in ICU, Hospital Seberang Jaya from October 2019 till October 2020 (n=32)

Characteristics	n (%)	median (IQR)
Gender		
Male	20 (62.5)	
Female	12 (37.5)	
Race		
Malay	25 (78.1)	
Chinese	4 (12.5)	
Indian	3 (9.4)	
Presence of comorbidities		
No	17 (53.1)	
Yes	15 (46.9)	
Presence of sepsis		
No	3 (9.4)	

Yes	29 (90.6)	
Type of infection		
Empiric	31 (96.9)	
Targeted	1 (3.1)	
Types of broader spectrum antibiotics used		
Meropenem	27 (84.4)	
Imipenem/ Cilastatin	3 (9.4)	
Vancomycin	2 (6.3)	
Types of narrower spectrum antibiotics used		
Piperacillin-tazobactam	11 (34.4)	
Cefepime	6 (18.8)	
Ampicillin- sulbactam	5 (15.6)	
Amoxicillin- clavulanic acid	3 (9.4)	
Ceftriaxone	2 (6.3)	
Others	5 (15.6)	
Sepsis free after treatment in ICU		
No	11 (34.4)	
Yes	21 (65.6)	
Survival Upon Discharge		
No	10 (31.3)	
Yes	22 (68.8)	
(Length of ICU stay (days		9.0 (10.00)
(Length of hospitalization (days		18.5 (17.00)
Mortality post 30 days		
No	21 (65.5)	
Yes	11 (34.4)	
Hospital readmission post 30 days		
No	32 (100)	

Note: IQR = Interquartile range

Sepsis free after treatment

Among the 32 patients, 29 (90.6%) of them presented with sepsis upon admission whereas 3 (9.4%) patients were sepsis free. Nevertheless, about 21 (65.6%) patients were sepsis free after being treated in ICU and remaining 11 (34.4%) were still treated as sepsis. Overall, only 6 (28.6%) patients were sepsis after the treatment in ICU presented with comorbidities compared to 15 (71.4%) patients who had no comorbidities. On the other hand, out of 11 patients yet to be sepsis free, 9 (81.8%) had comorbidities and remaining 2 (18.2%) had none (Table 2).

Table 2: Comparison of the laboratory parameters and conditions of patients in ICU, Hospital Seberang Jaya from October 2019 till October 2020 (n=32)

Laboratory parameters	**Pre-intervention**	**Post-intervention**	***p-value***
	median (Interquartile)	**median (Interquartile)**	
Creatinine (μmol/L)	133.5 (92.00-290.75)	106.0 (84.25-292.75)	0.459
Haemoglobin (g/dL)	9.8 (8.13-13.45)	9.7 (8.68-10.90)	0.935
Arterial blood pH	7.4 (7.29-7.42)	7.4 (7.19-7.42)	0.231
Albumin (g/L)	22.0 (17.00-27.00)	20.0 (16.25-23.00)	*0.021
Respiratory rate (breaths per minute)	24.0 (21.00-24.75)	20.0 (19.00-26.50)	*0.044
Systolic blood pressure (mmHg)	122.0 (109.00-129.00)	121.0 (94.00-128.25)	*0.018
Heart rate (beats per minute)	78.5 (74.00-95.75)	74.0 (65.00-80.50)	*0.010
Condition	**n (%)**	**n (%)**	
Requiring blood transfusion			0.065
No	19 (90.5)	7 (63.6)	
Yes	2 (9.5)	4 (36.4)	
Tachycardia			0.361
No	21(91.3)	9 (100.0)	
Yes	2 (8.7)	0	

Note: Paired t-test and Pearson's chi-square test for independence.

**p value<0.05*

Survival upon discharge

Majority of the study population survived upon discharge precisely 22 patients (68.8%). About 16 patients (72.7%) who had no comorbidities survived the hospital stay compared to 6 of them (24.3%) who had comorbidities. On the other hand, 9 patients (90%) with underlying comorbidities succumbed to death compared to 1 patient (10%) who had no comorbidities. Apart from this, the associated median length of ICU stay and overall hospitalization were 9 and 18.5 days respectively (Table 3).

Table 3: Association between presence of comorbidities and parameters of patients in ICU, Hospital Seberang Jaya from October 2019 till October 2020 (n=32)

Parameters	**Presence of comorbidities**		***p-value***
	No, n (%)	**Yes, n (%)**	
Sepsis free after treatment in ICU			*0.004
No	2 (18.2)	9 (81.8)	
Yes	15 (71.4)	6 (28.6)	
Survival upon discharge			*0.001
No	1 (10.0)	9 (90.0)	
Yes	16 (72.7)	6 (27.3)	
Mortality post 30 days			*0.004
No	15 (71.4)	6 (28.6)	
Yes	2 (18.2)	9 (81.8)	

Note: [a]Pearson's chi-square test for independence.

**p* value<0.05

Readmission within 30 days

All 22 patients had no history of readmission within 30 days after being discharge.

Mortality post 30 days

Only 1 patient died additionally post 30 days from the date of discharge accumulating the total number of fatalities up to 11 (34.4%). Among the patients died, only 9 patients (81.8%) had comorbidities whereas 2 patients (18.2%) had none.

Cost-savings

The total cost savings was approximately 52.7% which is equivalent to MYR 5,174.47 (p = 0.001). Prior to de-escalation of therapy, the mean antibiotics cost was MYR 306.94 whereas the calculated mean cost after the de-escalation of therapy was MYR 145.03 (Table 4).

Table 4: Cost before escalation versus cost after de-escalation of therapy for patients in ICU, Hospital Seberang Jaya from October 2019 till October 2020 (n=32)

	Cost before escalation	**Cost after de-escalation**	***p-value***
	(mean (±SD	**(mean (±SD**	
Cost of antibiotics, MYR	(±203.90) 306.94	(±130.77) 145.03	**0.001>*

Note: Paired t-test for independence.

**p value<0.05*

Discussion

De-escalation of antibiotics has always been an unfavorable decision as it is associated with higher mortality regardless of the patients' prognosis. In critically ill patients, the sepsis paradigm indeed suggests that 'hit it hard and hit it early'. It has been a norm to prescribe a broader spectrum antibiotics in patients look fairly ill upon presentation to the intensive care units having said that mortality matters the most at that point of time. This justification has to be reviewed promptly as mortality associated with bacterial resistance has become a threatening global issue. De-escalation is encouraged as a means to limit selective pressure via collateral damage induced by broader spectrum antibiotics [7]. Unfortunately, certain bacteria like extended spectrum beta lactamase *Escherichia coli* (ESBL *E. coli*) which is a known hospital acquired pathogen is found to be emerging within the community itself. This consequently reveals that we have limited number of effective antibiotic choices in near future [3]. In a way to respond to this threat, antimicrobial stewardship has become a holistic approach worldwide towards the judicious use antimicrobials and also to combat antimicrobial resistant. De-escalation is the epitome of the antimicrobial stewardship context. Therefore, this study has significantly evidenced that de-escalation of therapy is still safe even in critically ill patients as de-escalation is considered only for those patients who clinically improve post 72 hours after administrating broader spectrum of antibiotics. Similar findings were also concluded by Joffe (2008) and Kollef (2006) [9,10].

There are many factors considered prior to de-escalation of antibiotic therapy in this study. These include culture results post 72 hours of incubation, temperature, vital signs, white blood cell (WBC) count, C-reactive protein (CRP), source of infection, measures taken for source control, the local antibiogram, ventilator settings, radiological findings and the overall condition of the patients themselves [11,12]. But again every factor is subjective and varies for each patients depending on the infections being treated and the resulting complications [13].

This retrospective study has significantly validated that certain parameters such as respiratory rate, systolic blood pressure, heart rate and albumin had the similar outcomes when it is compared between pre and post intervention being made regardless of its antibiotics' indication. This further strengthens the fact that de-escalation of therapy is practically safe in culture negative scenarios and it does not affect the vital signs justly. A study by Eachempati, 2009 also concludes the same findings but focusing on a specific population of critically ill surgical patients diagnosed with VAP [8].

Adding to this, the condition of acute kidney injury (AKI) was noted to be improved after the de-escalation of therapy has been made which could be possibly attributed by using narrower spectrum antibiotics known to be lesser nephrotoxic compared to broader spectrum antibiotics. Routsi, 2020 also had very much similar finding on the kidney function. The significantly acceptable median albumin level between the intervention

phases explains that fluid balance was maintained adequately during the sepsis and de-escalation of therapy did not affect the recovery process in any circumstances. The median hemoglobin level remains almost the same during pre and post intervention phases. Perhaps this elucidates that the sepsis condition remains status quo despite de-escalation of therapy was made and may not necessitate to use broader spectrum of antibiotics [14].

Besides that, presence of comorbidities is found to be a vital and noteworthy confounding factor in determining the sepsis free after treatment, survival upon discharge and mortality post 30 days. Another way to interpret is patients presented with no comorbidities have greater opportunity to survive the sepsis compared to those with comorbidities. The comorbidities analyzed in this study population are diabetes mellitus (DM), hypertension, ischemic heart disease (IHD), dyslipidemia, rheumatoid arthritis and cerebrovascular accident (CVA). Other studies that found the same findings are Masterton (2011), Rello, *et al*. (2004), Soo Hoo, *et al*. (2005) and Kollef (2006) [6, 10, 15, 16].

On the other hand, de-escalation of therapy has a positive impact on the cost involved in the overall healthcare system. The total savings up to 52.7% was associated with the cost of the antibiotics only. An inclusive reduction in indirect financial burden was noticed thereafter. Another study by Masterton, 2011 agreed that de-escalation of antibiotics therapy is proven to be cost-effective including the probable reduced complications resulting in shortening the length of hospital stay [6]. A detailed study should be carried out to analyze the direct and indirect cost savings resulting from the de-escalation of therapy being made.

Conclusion

Through this study, it is proven that de-escalation of antibiotics therapy is not associated with increased risk of mortality despite no positive culture even in critically ill patients. Therefore, it is safer to de-escalate if patient is well clinically and with improving septic parameters despite presence of comorbidities rather than prescribing with a broader spectrum of antibiotics for the satisfaction of the treating medical practitioners.

Strengths and Limitations

The main strength of this study is that it was conducted at the site whereby highlighted as highest user for quite a number of broader spectrum antibiotics such as Meropenem, Piperacillin-tazobactam and Cefepime at national level. However, the drawback of this study are being a single center study and perhaps requires larger sample size to see the significant impact as a whole instead of generalization of study results.

Data Availability Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics Statement

This study involving human participants were reviewed and approved by MREC. Written informed consent for participation was not required for this study in accordance with the national legislation and institutional requirements.

Author Contributions

All authors listed have made a substantial, direct and intellectual contribution to the work and approved it for publication.

Acknowledgement

We would like to take this opportunity to thank the Director General of Health for his support and permission to publish this article. The authors declare no conflict of interest.

References

1. SHEA (2012) Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). Infection control and hospital epidemiology 33: 322-7.

2. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, et al. (2009) Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 48: 1-12.

3. Theuretzbacher U (2009) Future antibiotics scenarios: is the tide starting to turn? International journal of antimicrobial agents 34: 15-20.

4. Owens RC (2008) Antimicrobial stewardship: concepts and strategies in the 21st century. Diagnostic microbiology and infectious disease 61: 110-28.

5. MacDougall C, Polk RE (2005) Antimicrobial stewardship programs in health care systems. Clinical microbiology reviews 18: 638-56.

6. Masterton RG (2011) Antibiotic de-escalation. Critical care clinics 27: 149-62.

7. De Waele JJ, Ravyts M, Depuydt P, Blot SI, Decruyenaere J, et al. (2010) De-escalation after empirical meropenem treatment in the intensive care unit: fiction or reality? Journal of critical care 25: 641-6.

8. Eachempati SR, Hydo LJ, Shou J, Barie PS (2009) Does de-escalation of antibiotic therapy for ventilator-associated pneumonia affect the likelihood of recurrent pneumonia or mortality in critically ill surgical patients? The J trauma 66: 1343-8.

9. Joffe AR, Muscedere J, Marshall JC, Su Y, Heyland DK (2008) The safety of targeted antibiotic therapy for ventilator-associated pneumonia: a multicenter observational study. J critical care 23: 82-90.

10. Kollef MH, Morrow LE, Niederman MS, Leeper KV, Anzueto A, et al. (2006) Clinical characteristics and treatment patterns among patients with ventilator-associated pneumonia. Chest 129: 1210-8.

11. Depuydt P, Blot S (2007) Antibiotic therapy for ventilator-associated pneumonia: de-escalation in the real world. Critical care medicine 35: 632-3.

12. Rello J, Sa-Borges M, Correa H, Leal SR, Baraibar J () Variations in etiology of ventilator-associated pneumonia across four treatment sites: implications for antimicrobial prescribing practices. American J respiratory and critical care med 160: 608-13.

13. Blot S, De Waele JJ (2005) Critical issues in the clinical management of complicated intra-abdominal infections. Drugs 65: 1611-20.

14. Routsi C, Gkoufa A, Arvaniti K, Kokkoris S, Tourtoglou A, et al. (2020) De-escalation of antimicrobial therapy in ICU settings with high prevalence of multidrug-resistant bacteria: a multicentre prospective observational cohort study in patients with sepsis or septic shock. J Antimicrobial Chemotherapy 75: 3665-74.

15. Rello J, Vidaur L, Sandiumenge A, Rodríguez A, Gualis B, Boque C, et al. (2004) De-escalation therapy in ventilator-associated pneumonia. Critical care medicine 32: 2183-90.

16. Soo Hoo GW, Wen YE, Nguyen TV, Goetz MB (2005) Impact of clinical guidelines in the management of severe hospital-acquired pneumonia. Chest 128: 2778-87.