Senses Sci (Educ Sci Tech) 2022: 9 (3) 1650-1667
doi: 10.14616/sands-2022-3-16501667

Article

The psychological impact of gut-brain-axis modulation by broad spectrum antibiotics in acute leukemia patients treated with Larson induction protocol: a cross-sectional study

Sami Hussein Mahmoud Hammadi, Azza Mohamed Baraka, Salma Hany Kandiel

Clinical Pharmacology Department, Faculty of Medicine, Alexandria University, Egypt.

*Correspondence: Salma Hany Kandiel, El Mowasah Educational and Medical Complex, Alexandria, Egypt. Tel: +201000917456. Email: salma.kandiel@gmail.com

Abstract. *Background*: Individual responses to a particular drug differ enormously in terms of efficacy as well as safety. In contrast to the human genome, gut microbial composition can be altered, making it an appealing target for enhancing therapeutic efficacy and safety. Antibiotic consumption deeply affects the composition of microflora. Perturbations of gut microbial ecology may trigger or exacerbate neuro-inflammation and behavioral comorbidities following chemotherapy. This study explored the possible impact of gut-brain axis modulation by broad spectrum antibiotics on the psychological status among hospitalized acute lymphoblastic leukemia (ALL) patients undergoing treatment with Larson induction chemotherapy protocol.

Methods: A cross sectional survey was conducted on 60 ALL patients undergoing treatment with Larson induction chemotherapy protocol and broad spectrum antibiotics. Patients were recruited from Internal medicine (Clinical Hematology Unit), Alexandria university hospital. In order to assess the depression and anxiety status we used a validated Arabic version of the Hospital Anxiety and Depression Scale (HADS).

Results: Among the studied cases 31.7% had normal depression score, (16.7%) had borderline depression score and (51.7%) had abnormal depression score. Meanwhile, (43.3%) had normal anxiety score, (33.3%) had borderline anxiety score and (23.3%) had abnormal anxiety score. A significant relation between both scores; depression and anxiety was detected among the studied patients (χ^2=24.962, ^{MC}p =<0.001). In addition, there was a significant increase in the duration of

antibiotic therapy in patients having both borderline and abnormal depression/anxiety scores in comparison to patients with normal depression/anxiety scores. However, no significant difference was detected in the duration of antibiotic therapy between patients having borderline and abnormal depression/anxiety scores (H=33.097, p1=0.012, p2<0.001, p3=0.055) (H=20.460, p1<0.001, p2<0.001, p3=0.552). *Conclusions*: Antibiotic use, specially the broad-spectrum type, for long duration, was associated with an increased risk of psychiatric problems.

Keywords: Antibiotics, Gut-Brain-Microbiome axis, Chemotherapy, Leukemia, HADs.

Introduction

Individual responses to a particular drug differ enormously both in terms of efficacy as well as safety. Almost half of the treated patients receive no benefit from their therapy. Moreover, many of them suffer from adverse drug reactions (ADRs). (1,2) Pharmacogenomics has been at the forefront of research to face this problem through exploring the effect of genetics on drug safety and efficacy. However, genetic factors solely were found to be inadequate to fully explain the detected variation. (3) Recently the gut microbiome, which is sometimes called the second genome, was detected as a respected player in this aspect. (4)

The human body is an ecosystem hosting approximately 100 trillion organisms that live primarily, though not exclusively, within the gut. Microbiome comprises the largest surface area of microbial interplay with host immune system. (5,6) It exists in a dynamic equilibrium between eubiosis and dysbiosis in a way that impacts almost every aspect of host physiology.(7) The microbiome can be considered as a signaling hub that incorporates environmental inputs with genetic and immune signals to influence the host's immunity, metabolism, development, and even behavior. (8) Perturbations of gut microbial composition and function have been incriminated in many chronic diseases, such as metabolic syndrome, immune maladaptation and various central nervous system (CNS) diseases. (9) Dysbiosis is influenced by many factors, such as physical and psychological stresses, antibiotic treatment, chemotherapy, radiation, ageing, and diet. (10) Antibiotic consumption deeply affects the composition of microflora. (11)

Accumulating evidence unveils the role of gut microbiota in outlining cancer chemo/ immunotherapeutic efficacy and toxicity. (12) Cognitive impairment due to chemotherapy is an ill-defined complication. It has a substantial psycho-social burden on cancer survivors and a massive influence on daily living activities. (13) The pathophysiology has not been clearly defined; however, candidate mechanisms may be linked to neuro-inflammation. (14) Perturbations of gut microbial ecology following chemotherapy may trigger or exacerbate neuro-inflammation and behavioral comorbidities. (15)

Gut brain communication (The Gut-Brain Axis)

Although gut and brain seem to be disparate, they are intimately connected. A bidirectional communication exists between the mini brain of the gut; the enteric nervous system (ENS), and the CNS in order to optimize the functioning in both systems. It is thought that gut microbiota can

initiate and modify much of this cross talk. (16) Pathways involved in this connection between microbiota and the brain include: a) The endocrine through the action of cortisol hormone. b) The neural pathway with the contribution of the vagus and the ENS. c) The immune pathway where signaling occurs via inflammatory cytokines. d) The biochemical pathway via bacterial metabolites; short-chain fatty acids (SCFAs). (17,18) These complex two-way communication pathways between the brain and the gut with its inhabitant microbiota preserve homeostasis in all of them. (19,20)

Based on what was mentioned earlier, it can be suggested that the pharmacological modulation of gut microflora displays a significant potential as an adjuvant to adjust the therapeutic index of cancer chemotherapy. In the light of this, our study explored the possible impact of gut-brain axis modulation by broad spectrum antibiotics on depression and/or anxiety status among hospitalized acute lymphoblastic leukemia (ALL) patients undergoing treatment with Larson induction chemotherapy protocol.

Methods

A descriptive cross-sectional study was carried on adult ALL patients after approval of the ethical committee of Alexandria Faculty of medicine (IRB No.: 00012098-FWA No.: 00018699). Sample size was calculated with Power Analysis and Sample Size Software (PASS 2020) "NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass".(21) A minimal total hypothesized sample size of 60 patients was needed to explore the status of depression and/or anxiety among ALL patients undergoing treatment with Larson induction chemotherapy protocol and antibiotics of different spectrum; taking into consideration 95% confidence level, effect size of 17% and 5% precision using Z-test.(22)

Patients were recruited from Internal medicine (Clinical Hematology Unit), Alexandria university hospital; as a part of the antimicrobial stewardship program. This program was conducted to optimize antimicrobial use among hospitalized patients in order to improve clinical outcomes.

Inclusion criteria for patients were in the form of:

1. Males and females aged 18 to 65 years.
2. Hospitalized acute lymphoblastic leukemia patients undergoing treatment with Larson induction Chemotherapy protocol.(23)
3. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2. (24)
4. Patients receiving broad spectrum antibiotics either prophylactically or therapeutically.

Meanwhile, we excluded:

1. Patients with history of mental illness before the administration of chemotherapy.
2. Patients using antidepressants or anxiolytics.
3. Patients with evidence of brain metastasis or other structural brain lesions.

4. Patients with evidence of any structural gastrointestinal lesion.

Data were collected through face to face interviews with patients admitted to the hematology ward. Patient treatment information and cancer diagnosis were collected from patients' medical records after hospital permission. Before enrollment, eligible participants were informed of the study purpose and their rights and informed consent was taken from the patients.

The depression and/or anxiety state in these patients was assessed and compared. We used a validated Arabic version of the Hospital Anxiety and Depression Scale (HADS) for this purpose.(25)

Hospital Anxiety and Depression Scale

The HADS is a fourteen item questionnaire composed of two subscales one for depression and the other for anxiety in the form of four-point Likert-type scales. For both anxiety and depression, the subscales range from 0 to 21. The final scores of HADS were subdivided into three categories:

- From 0 to 7 was considered as normal.
- From 8 to 10 was considered as borderline.
- From 11 to 21 was considered as abnormal.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov-Smirnov test was used to verify the normality of distribution.

Qualitative data were described using number and percent. Quantitative data were described using median and range (minimum & maximum). Significance of the obtained results was judged at the 5% level.

The used tests were:

1. Chi-square test; for categorical variables, to compare between different groups.
2. Monte Carlo correction; for chi-square when more than 20% of the cells have expected count less than 5.
3. Kruskal Wallis test; for not normally distributed quantitative variables, to compare between more than two studied groups and Post Hoc (Dunn's multiple comparisons test) for pairwise comparisons.
4. Spearman coefficient; to correlate between two not normally distributed quantitative variables.

Results

1. Distribution of the studied cases according to demographic data and duration antibiotic therapy (Table 1)

A. Demographic data

Table 1 shows the characteristics of the patients in our study. A total of 60 patients completed the survey; 55% were males and 45% were females. Forty percent of the patients were between the ages of 18 and 25 years. Most patients (63.3%) were employed, (48.3%) had middle or secondary school education and about (43.3%) of them were single.

Table 1: Distribution of the patients according to demographics and duration of antibiotic therapy (n = 60)

	Frequency (%)
Sex	
Male	33 (55%)
Female	27 (45%)
Age (years)	
18 – 25	24 (40%)
26 – 35	15 (25%)
36 – 45	13 (21.7%)
46 – 55	6 (10%)
56 – 65	2 (3.3%)
Employment	
Employed	38 (63.3%)
Unemployed	22 (36.7%)
Education	
Primary school or below	6 (10%)
Middle or secondary school	29 (48.3%)
University or higher	25 (41.7%)

Marital Status	
Single	26 (43.3%)
Married	25 (41.7%)
Divorced	6 (10%)
Widowed	3 (5%)
Residency	
Urban	30 (50%)
Rural	30 (50%)
Duration of Antibiotic Therapy (Days)	
1 – 7	12 (20%)
8 –14	28 (46.7%)
15 –21	14 (23.3%)
22 –28	6 (10%)

Duration of antibiotic therapy

Most of our patients used antibiotics for a duration between (8 –14) days (46.7%). Meanwhile, (23.3%) used antibiotics for (15 –21) days and (20%) used it for (22 –28) days.

Distribution of depression and anxiety in hospitalized ALL patients undergoing treatment with Larson induction Regimen and broad spectrum antibiotics (table 2, figure 1)

Among the studied cases 19 (31.7%) had normal depression score (0-7), 10 (16.7%) had borderline depression score (8-10) and 31 (51.7%) had abnormal depression score (11-21). On the other hand, 26 patients (43.3%) had normal anxiety score, 20 patients (33.3%) had borderline anxiety score and 14 patients (23.3%) had abnormal anxiety score.

Table 2: Distribution of depression and anxiety in hospitalized ALL patients undergoing treatment with Larson induction Regimen and broad spectrum antibiotics (n = 60)

	Frequency (%) of Depression	Frequency (%) of Anxiety
Normal= score (0-7)	19 (31.7)	26 (43.3)
Borderline= score (8-10)	10 (16.7)	20 (33.3)
Abnormal =score (11-21)	31 (51.7)	14 (23.3)

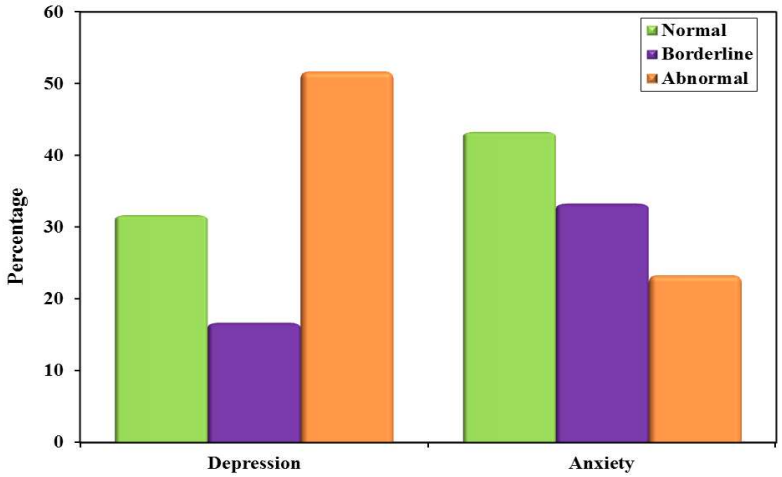


Figure 1: Distribution of depression and anxiety in hospitalized ALL patients undergoing treatment with Larson induction Regimen and broad spectrum antibiotics (n = 60)

Depression and anxiety status in relation to sociodemographic variables of the studied patients (table 3)

Depression scores were higher in males, patients aged (18–35) years, employed, middle or secondary school educated patients and patients living in urban areas. However, no statistically significant association was found between depression and sociodemographic variables except for the age (χ^2=14.633, ^{MC}p = 0.030).

Meanwhile, anxiety scores were higher in males, patients aged (36 –45) years, unemployed, patients with higher education and married. However, no statistically significant association was found between anxiety scores and sociodemographic variables.

Table 3: Depression and anxiety status in relation to sociodemographic variables

	Depression			χ^2 (p)	Anxiety			χ^2 (p)
	Normal (n = 19)	Borderline (n = 10)	Abnormal (n = 31)		Normal (n = 26)	Borderline (n = 20)	Abnormal (n = 14)	
Sex								
Male	8 (42.1%)	8 (80.0%)	17 (54.8%)	3.802 (0.149)	13 (50.0%)	11 (55.0%)	9 (64.3%)	0.750 (0.687)
Female	11 (57.9%)	2 (20.0%)	14 (45.2%)		13 (50.0%)	9 (45.0%)	5 (35.7%)	
Age (years)								
18 – 25	10 (52.6%)	3 (30.0%)	11 (35.5%)	14.633* (^{MC}p= 0.030*)	14 (53.8%)	6 (30.0%)	4 (28.6%)	8.010 (^{MC}p= 0.393)
26 – 35	1 (5.3%)	2 (20.0%)	12 (38.7%)		5 (19.2%)	7 (35.0%)	3 (21.4%)	
36 – 45	6 (31.6%)	1 (10.0%)	6 (19.4%)		4 (15.4%)	3 (15.0%)	6 (42.9%)	
46 – 55	2 (10.5%)	3 (30.0%)	1 (3.2%)		2 (7.7%)	3 (15.0%)	1 (7.1%)	
56 – 65	0 (0.0%)	1 (10.0%)	1 (3.2%)		1 (3.8%)	1 (5.0%)	0 (0.0%)	
Employment								
Employed	15 (78.9%)	4 (40.0%)	19 (61.3%)	4.395 (0.111)	20 (76.9%)	12 (60.0%)	6 (42.9%)	4.691 (0.096)
Unemployed	4 (21.1%)	6 (60.0%)	12 (38.7%)		6 (23.1%)	8 (40.0%)	8 (57.1%)	
Education								
Primary school or below	1 (5.3%)	3 (30.0%)	2 (6.5%)	6.223 (^{MC}p=0.153)	1 (3.8%)	3 (15.0%)	2 (14.3%)	3.102 (^{MC}p=0.564)
Middle or secondary school	11 (57.9%)	2 (20.0%)	16 (51.6%)		14 (53.8%)	10 (50.0%)	5 (35.7%)	
University or higher education	7 (36.8%)	5 (50.0%)	13 (41.9%)		11 (42.3%)	7 (35.0%)	7 (50.0%)	
Marital Status								
Single	8 (42.1%)	4 (40.0%)	14 (45.2%)	4.950 (^{MC}p= 0.530)	13 (50.0%)	8 (40.0%)	5 (35.7%)	6.043 (^{MC}p= 0.387)
Married	7 (36.8%)	5 (50.0%)	13 (41.9%)		9 (34.6%)	8 (40.0%)	8 (57.1%)	
Divorced	4 (21.1%)	0 (0.0%)	2 (6.5%)		4 (15.4%)	2 (10.0%)	0 (0.0%)	
Widowed	0 (0.0%)	1 (10.0%)	2 (6.5%)		0 (0.0%)	2 (10.0%)	1 (7.1%)	
Residency								

					Gut-brain-axis modulation & Chemotherapy			
Urban	8 (42.1%)	5 (50.0%)	17 (54.8%)	0.764 (0.682)	12 (46.2%)	11 (55.0%)	7 (50.0%)	0.354 (0.838)
Rural	11 (57.9%)	5 (50.0%)	14 (45.2%)		14 (53.8%)	9 (45.0%)	7 (50.0%)	

χ^2: Chi square test MC: Monte Carlo

p: p value for comparing between depression and anxiety score

*: Statistically significant at $p \leq 0.05$

Relation between depression and anxiety scores in the studied patients (table 4, figure 2)

Among the 19 patients who had normal depression score 17 patients (89.5%) had a normal anxiety score, 1 patient (5.3%) had a borderline anxiety score and 1 patient (5.3%) had abnormal anxiety score.

Meanwhile, among the 10 patients with borderline depression score, 3 patients (30%) had normal anxiety score, 5 patients (50%) had borderline anxiety score and 2 patients (20%) had abnormal anxiety score.

Regarding the 31 patients who had abnormal depression score, 6 patients (19.4%) had normal anxiety scale, 14 patients (45.2%) had borderline anxiety scale, and 11 patients (35.5%) had abnormal anxiety score too.

A significant relation between both scores; depression and anxiety was detected among the studied patients (χ^2=24.962, ^{MC}p =<0.001).

Table 4: Relation between depression and anxiety scores in the studied patients (n = 60)

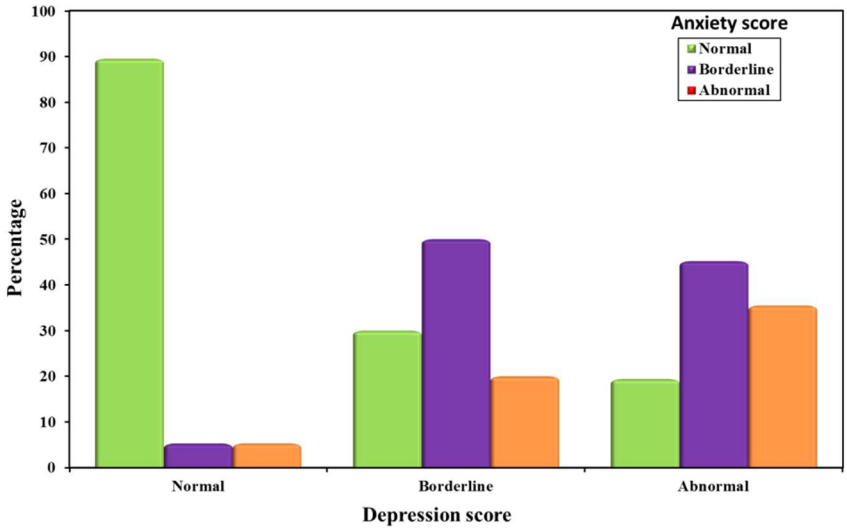
Anxiety score	**Depression score**						**χ^2**	**^{MC}p**
	0-7 = Normal (n = 19)		**8-10 = Borderline (n = 10)**		**11-21 = abnormal (n = 31)**			
	No.	**%**	**No.**	**%**	**No.**	**%**		
0-7 = Normal	17	89.5	3	30.0	6	19.4		
8-10 = Borderline	1	5.3	5	50.0	14	45.2	24.962*	<0.001*
11-21 = Abnormal	1	5.3	2	20.0	11	35.5		

χ^2: Chi square test MC: Monte Carlo

p: p value for comparing between depression and anxiety score

*: Statistically significant at $p \leq 0.05$

Figure 2: Relation between depression and anxiety scores in the studied patients (n = 60)



Correlation between depression and anxiety scores in the studied patients

The depression score had a strong positive association with the anxiety score among the studied patients (rs=0.666, p < 0.001) (Table 5, Figure 3).

Table 5: Correlation between depression and anxiety scores (n = 60)

	r_s	P
Depression vs. anxiety scores	0.666	<0.001*

r_s: Spearman coefficient

*: Statistically significant at p ≤ 0.05

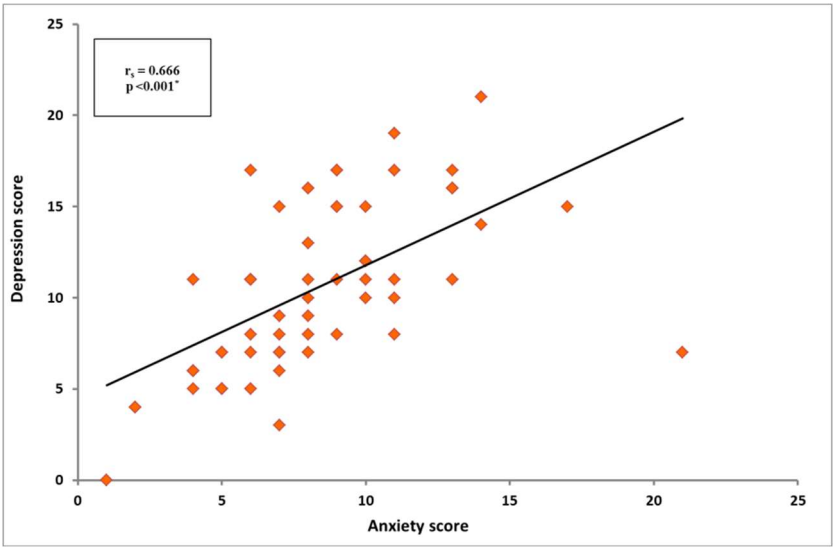


Figure 3: Correlation between depression and anxiety scores (n = 60)

Relation between depression / anxiety scores and the duration of antibiotic therapy in hospitalized ALL patients undergoing treatment with Larson induction Regimen and broad spectrum antibiotics (Table 6, figures 4,5)

The median duration of antibiotic therapy was 5.0 (2.0 – 15.0) days in patients with normal depression score, 11.50 (9.0 – 20.0) days in patients with borderline depression score, and 16.0 (7.0 – 26.0) days in patients with abnormal depression score. There was a significant increase in the duration of antibiotic therapy in patients having both borderline and abnormal depression scores in comparison to patients with normal depression score. But no significant difference was detected in the duration of antibiotic therapy between patients having borderline and abnormal depression score. (H=33.097, p1=0.012, p2<0.001, p3=0.055).

Meanwhile, the median duration of antibiotic therapy was 10.0 (2.0 – 23.0) days in patients having normal anxiety score, 14.0 (9.0 – 26.0) days in patients with borderline anxiety score, and 17.0 (7.0 – 25.0) days in patients with abnormal anxiety score. There was a significant increase in the duration of antibiotic therapy in patients having both borderline and abnormal anxiety scores in comparison to patients with normal anxiety score. However, no significant difference was detected in the duration of antibiotic therapy between patients having borderline and abnormal anxiety score. (H=20.460, p1<0.001, p2<0.001, p3=0.552).

Table 6: Relation between depression / anxiety scores and the duration of antibiotic therapy (n = 60)

	N	Duration antibiotic therapy (d) Median (Min. – Max.)	H	P	Sig. bet. categories
Depression					
0-7 = Normal	**19**	5.0 (2.0 –15.0)			p1=0.012*
8-10 = borderline	**10**	11.50 (9.0 –20.0)	33.097*	<0.001*	p2<0.001*
11-21 =abnormal	**31**	16.0 (7.0 –26.0)			p3=0.055
Anxiety					
0-7 = Normal	**26**	10.0 (2.0 –23.0)			p1<0.001*
8-10 = borderline	**20**	14.0 (9.0 –26.0)	20.460*	<0.001*	p2<0.001*
11-21 =abnormal	**14**	17.0 (7.0 –25.0)			p3=0.552

H: H for **Kruskal Wallis test,** Pairwise comparison bet. each 2 groups was done using **Post Hoc Test (Dunn's for multiple comparisons test)**

p: p value for comparing the different categories

p1: p value for comparing between **Normal** and **borderline**

p2: p value for comparing between **Normal** and **Abnormal**

p3: p value for comparing between **borderline** and **abnormal**

*: Statistically significant at $p \leq 0.05$

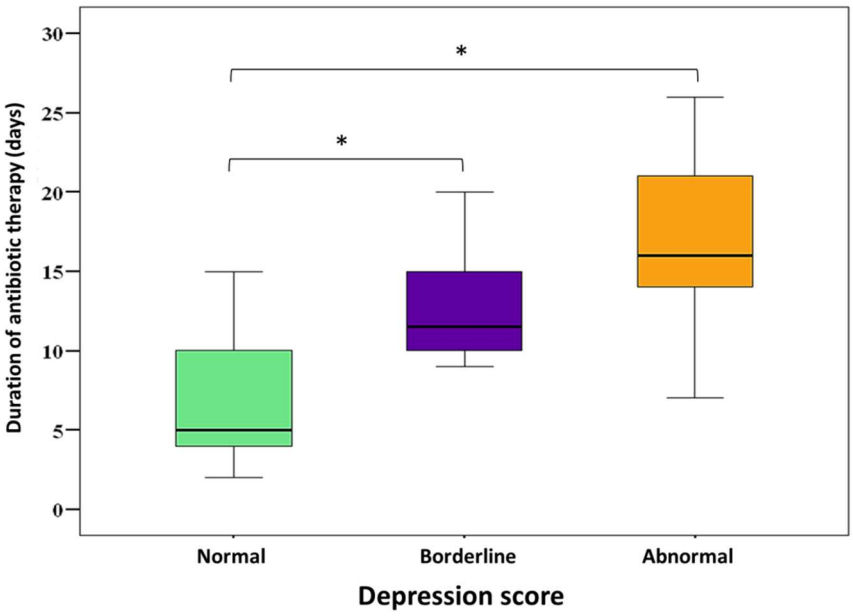


Figure 4: Relation between depression score and the duration of antibiotic therapy (n = 60).

*: Statistically significant at $p \leq 0.05$

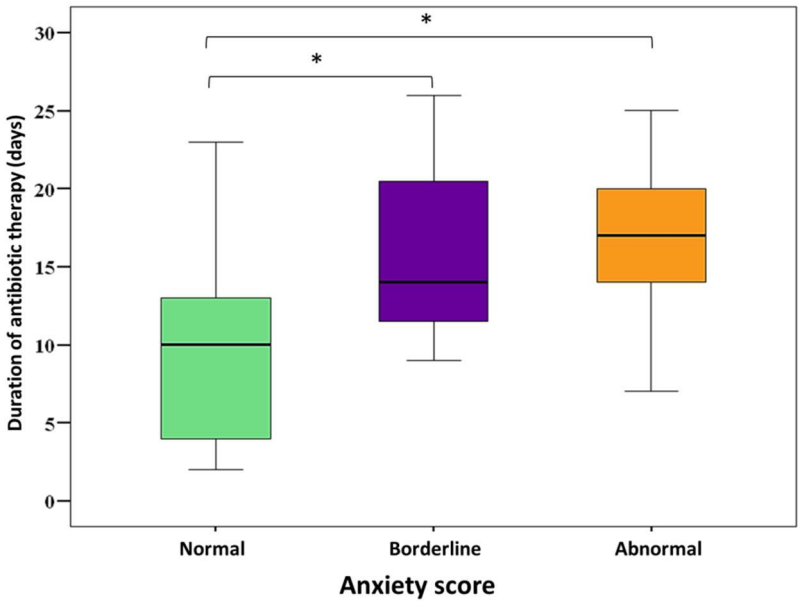


Figure 5: Relation between anxiety score and the duration of antibiotic therapy (n = 60)

*: Statistically significant at $p \leq 0.05$

Discussion

Cancer is a global health burden, and despite the ongoing improvement in medical therapeutics, resistance and side effects continue to be prominent factors causing treatment limitation. A rising body of research shows a bidirectional relationship between microbiota and the therapeutic profile of cancer chemotherapy. This gave rise to the concept of "pharmacomicrobiomics," a new field that studies how medications interact with microbiota.(12)
The microbiome is sometimes regarded as an organ that is intimately linked to its host in a perfect mutualistic manner; at the endocrine, metabolic, immune, and neural levels. But unlike actual host organs, microbiota can live in two opposing states; eubiosis and dysbiosis. The shift from eubiosis to dysbiosis has detrimental effects on the health of the host. (10) Antibiotics are a commonly used category of drugs in cancer patients; whether prophylactically or therapeutically. But unfortunately they are thought to be of the major disruptors of gut microbiota.(11)

The current study was conducted to explore the psychological impact in the form of depression and/or anxiety among hospitalized ALL patients undergoing treatment with Larson induction chemotherapy protocol and its relation to the duration of use of broad spectrum antibiotics.
We used HADS to screen our patients for anxiety and depression. It is a rapid self-reported screening scale that can assess anxiety and depression as 2 dimensions scored separately. HADS is a validated tool for use in cancer patients that can be used easily by patients because of the lack of questions about physical symptoms, which may cause confusion with depression and/or anxiety symptoms.(26) All these factors led to the high compliance of the patients to complete the questionnaire.

In this study, the rate of significant depression (borderline plus abnormal scores) was 68.4 % and the rate of significant anxiety was 56.6 %. A previous study in adult acute leukemia patients reported rates of significant depression (43.7%) and significant anxiety (50.7%).(27) These rates were much lower than our rates which could be attributable to the type of leukemia or the concomitant use of broad spectrum antibiotics in our study. Results also revealed a significant strong positive correlation between both anxiety and depression which goes with findings from Britain, where the majority of cancer patients who had depression had clinically significant anxiety symptoms as well.(28)

A significant association was found between both anxiety and depression in relation to the duration of antibiotic use in our patients. This association is supported by findings from some previous clinical studies which figured out the existence of an association between antibiotics and the risk of mental illness.(29, 30)
There is no doubt that antibiotics are lifesaving pharmacological tools since their discovery, however, the majority of these tools have multiple off-target effects. Apart from killing harmful bacteria, beneficial gut microbiota is also compromised. Broad-spectrum antibiotics prescribed only for one week can have long-term effects on gut microbiome.(31, 32)

Increasing evidence strengthens the view that mental illness is related to the decrease in microbial diversity.(33) A meta-analysis of 59 case-control studies conducted by Nikolova et al. detected that gut microbiota perturbations in the form of depletion of specific anti-inflammatory butyrate-forming species and overgrowth of pro-inflammatory species were associated with depression, bipolar disorder, schizophrenia, and anxiety.(34)

Gut microbiota are thought to play a role in the regulation of the HPA axis; the body's most influential stress system. This axis is incriminated in a variety of psychiatric diseases. It is well known that over activation of the HPA is linked to severe forms of depression. Given the fact that the gut bacteria and HPA are in bidirectional communication, it is not a surprise that antibiotics that affect the microbiota could also influence the HPA activity.(35) In addition, gut microbes are thought to produce major neurotransmitters. For example, lactobacilli can produce GABA(36) and Bifidobacteria are shown to increase blood tryptophan and regulate serotonin synthesis.(37)

Brain-derived neurotrophic factor (BDNF) is known to be altered in depressed patients and its levels are significantly lowered in germ-free animals that lack microbiota.(38) Also, in a rodent study, one of the third-generation cephalosporins; ceftriaxone was found to significantly alter gut microbiota and lower the BDNF levels in the hippocampus.(39)

Most of broad-spectrum antibiotics have a significant impact on SCFAs levels. It was found that a course of antibiotic treatment with either clindamycin or ampicillin in healthy adults can affect the abundance and colonization of gut microflora with subsequent significant reduction in the content of SCFAs.(40) In another study conducted by Romick-Rosendale et al.(41) in children undergoing hematopoietic stem cell transplantation they reported significant alterations in butyrate levels and other SCFAs on top of antibiotic exposure.

Antibiotics can also cause impairment in gut epithelial tight junctions resulting in barrier dysfunction which could be implicated in leaky gut syndrome. In such a condition molecules like lipopolysaccharide can enter the bloodstream and initiate inflammation leading to enhanced activation of the HPA, rendering these patients more vulnerable to mental illness.(42)

Limitations of the study:

Our results should be considered in the context of some limitations. First, our study was a cross-sectional study, so the causality cannot be concluded. Second, small sample size of the current study is due to restricted inpatient admissions during covid-19 pandemic. Third, this small hypothesized sample size highlights the importance of exploring the psychological impact of antibiotic use among cancer patients treated with chemotherapy. Further studies with large sample size are needed to determine the prevalence of depression, anxiety, and other psychometric factors among these patients.

Conclusions

Antibiotic use, specially the broad-spectrum type, for long duration, was associated with an increased risk of psychiatric problems. A deeper understanding of the microbiota-gut-brain axis may substantially aid in the prevention and treatment of psychological disorders in cancer patients.

Acknowledgements

Our great gratitude goes to Prof. Dr. Ibtissam Osman for her precious guidance and support. The authors are also especially grateful to Dr. Manal Bessa for her helpful instructions.

Data availability statement

Survey participants were given the assurance that the raw data would stay private and would not be disseminated because of the sensitive nature of the questions answered in this study.

Funding information

This research did not receive any specific grant from funding agencies in the public, commercial, or nonprofit organizations.

Conflict of interest

The authors declare that they have no conflicts of interest.

Ethics approval

This study was approved by the ethical committee of Alexandria Faculty of medicine.

Patient consent

Participants were informed of the study purpose and their rights and informed consent was taken from the patients.

References

1. Doestzada M, Vila AV, Zhernakova A, et al. Pharmacomicrobiomics: a novel route towards personalized medicine? Protein Cell. 2018;9(5):432-45.
2. Spear BB, Heath-Chiozzi M, Huff J. Clinical application of pharmacogenetics. Trends Mol Med. 2001;7(5):201-4.
3. Scott SA, Swen JJ. Pharmacogenomic Determinants of Interindividual Drug Response Variability: From Discovery to Implementation. Genes. 2021;12(3):393.
4. Taneja V. Microbiome: impact of gender on function & characteristics of gut microbiome. In: Legato M, (ed). Principles of Gender-Specific Medicine. London: Elsevier; 2017. 569-83.
5. Sender R, Fuchs S, Milo R. Are we really vastly outnumbered? Revisiting the ratio of bacterial to host cells in humans. Cell. 2016;164(3):337-40.
6. Qin J, Li R, Raes J, et al. A human gut microbial gene catalogue established by metagenomic sequencing. nature. 2010;464(7285):59-65.
7. Feng Q, Chen W-D, Wang Y-D. Gut microbiota: an integral moderator in health and disease. Front Microbiol. 2018;9:151.
8. Sharon G, Garg N, Debelius J, Knight R, Dorrestein PC, Mazmanian SK. Specialized metabolites from the microbiome in health and disease. Cell Metab. 2014;20(5):719-30.
9. Wang B, Yao M, Lv L, Ling Z, Li L. The human microbiota in health and disease. Engineering. 2017;3(1):71-82.
10. Weiss GA, Hennet T. Mechanisms and consequences of intestinal dysbiosis. Cell Mol Life Sci. 2017;74(16):2959-77.

11. Ramirez J, Guarner F, Bustos Fernandez L, Maruy A, Sdepanian VL, Cohen H. Antibiotics as major disruptors of gut microbiota. Front Cell Infect Microbiol. 2020;10:572912.
12. Panebianco C, Andriulli A, Pazienza V. Pharmacomicrobiomics: exploiting the drug-microbiota interactions in anticancer therapies. Microbiome. 2018;6(1):92.
13. Soliman A, Ibrahim R, Kotob M. Chemotherapy Induced Cognitive Impairment in Hematological Malignancies. Clin Lymphoma Myeloma Leuk. 2018;18:S191-S2.
14. Dietrich J, Prust M, Kaiser J. Chemotherapy, cognitive impairment and hippocampal toxicity. Neuroscience. 2015;309:224-32.
15. Luca M, Chattipakorn SC, Sriwichaiin S, Luca A. Cognitive-Behavioural Correlates of Dysbiosis: A Review. Int J Mol Sci. 2020;21(14):4834.
16. Rao M, Gershon MD. The bowel and beyond: the enteric nervous system in neurological disorders. Nature Reviews Gastroenterology & Hepatology. 2016;13(9):517-28.
17. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci. 2012;13(10):701-12.
18. Osadchiy V, Martin CR, Mayer EA. The gut-brain axis and the microbiome: mechanisms and clinical implications. Clin Gastroenterol Hepatol. 2018;17(2):322-32.
19. Subramaniam CB, Bowen JM, Gladman MA, Lustberg MB, Mayo SJ, Wardill HR. The microbiota-gut-brain axis: an emerging therapeutic target in chemotherapy-induced cognitive impairment. Neuroscience & Biobehavioral Reviews. 2020.
20. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol. 2015;28(2):203-9.
21. Nathan E. PASS: A quick and easy power and sample-size calculation program. Am Statistic. 1988;42(3):229.
22. Abuelgasim KA, Ahmed GY, Alqahtani JA, Alayed AM, Alaskar AS, Malik MA. Depression and anxiety in patients with hematological malignancies, prevalence, and associated factors. Saudi Med J. 2016;37(8):877-81.
23. Larson RA, Dodge RK, Burns CP, et al. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: cancer and leukemia group B study 8811. Blood. 1995;85(8):2025-37.
24. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-56.
25. Terkawi A, Tsang S, AlKahtani G, et al. Development and validation of Arabic version of the Hospital Anxiety and Depression Scale. Saudi J Anaesth. 2017;11(5):S11-S8.
26. Ballenger JC, Davidson JR, Lecrubier Y, Nutt DJ, Jones RD, Berard RM. Consensus statement on depression, anxiety, and oncology. J Clin Psychiatry. 2001;62:64-7.
27. Wang Y, Yan J, Chen J, et al. Comparison of the anxiety, depression and their relationship to quality of life among adult acute leukemia patients and their family caregivers: a cross-sectional study in China. Qual Life Res. 2021;30(7):1891-901.
28. Pitman A, Suleman S, Hyde N, Hodgkiss A. Depression and anxiety in patients with cancer. BMJ. 2018;361:k1415.

29. Lurie I, Yang Y-X, Haynes K, Mamtani R, Boursi B. Antibiotic exposure and the risk for depression, anxiety, or psychosis: a nested case-control study. J Clin Psychiatry. 2015;76(11):1522-8.
30. Hu K, Smedby KE, Sjölander A, et al. Use of antibiotics and risk of psychiatric disorders in newly diagnosed cancer patients: a population-based cohort study in Sweden. Cancer Epidemiol Biomarkers Prev. 2022;31(3):528-35.
31. Hao W-Z, Li X-J, Zhang P-W, Chen J-X. A review of antibiotics, depression, and the gut microbiome. Psychiatry Res. 2020;284:112691.
32. Dinan K, Dinan T. Antibiotics and mental health: The good, the bad and the ugly. J Intern Med. 2022.
33. Kelly JR, Borre Y, O'Brien C, et al. Transferring the blues: depression-associated gut microbiota induces neurobehavioural changes in the rat. J Psychiatr Res. 2016;82:109-18.
34. Nikolova VL, Hall MR, Hall LJ, Cleare AJ, Stone JM, Young AH. Perturbations in gut microbiota composition in psychiatric disorders: a review and meta-analysis. JAMA psychiatry. 2021;78(12):1343-54.
35. Wu W-L, Adame MD, Liou C-W, et al. Microbiota regulate social behaviour via stress response neurons in the brain. Nature. 2021;595(7867):409-14.
36. Patterson E, Ryan PM, Wiley N, et al. Gamma-aminobutyric acid-producing lactobacilli positively affect metabolism and depressive-like behaviour in a mouse model of metabolic syndrome. Sci Rep. 2019;9(1):16323.
37. Desbonnet L, Garrett L, Clarke G, Bienenstock J, Dinan TG. The probiotic Bifidobacteria infantis: an assessment of potential antidepressant properties in the rat. J Psychiatr Res. 2008;43(2):164-74.
38. Bercik P, Denou E, Collins J, et al. The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. Gastroenterology. 2011;141(2):599-609.
39. Zhao Z, Wang B, Mu L, et al. Long-term exposure to ceftriaxone sodium induces alteration of gut microbiota accompanied by abnormal behaviors in mice. Front Cell Infect Microbiol. 2020;10:258.
40. Høverstad T, Carlstedt-Duke B, Lingaas E, et al. Influence of ampicillin, clindamycin, and metronidazole on faecal excretion of short-chain fatty acids in healthy subjects. Scand J Gastroenterol. 1986;21(5):621-6.
41. Romick-Rosendale LE, Haslam DB, Lane A, et al. Antibiotic exposure and reduced short chain fatty acid production after hematopoietic stem cell transplant. Biol Blood Marrow Transplant. 2018;24(12):2418-24.
42. Feng Y, Huang Y, Wang Y, Wang P, Song H, Wang F. Antibiotics induced intestinal tight junction barrier dysfunction is associated with microbiota dysbiosis, activated NLRP3 inflammasome and autophagy. PloS one. 2019;14(6):e0218384.