НИРКИ KIDNEYS

DOI: https://doi.org/10.22141/2307-1257.14.3.2025.533

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Immune response on interferon-gamma in rats infected with *C.albicans*

For citation: Kidneys. 2025;14(3):207-213. doi: 10.22141/2307-1257.14.3.2025.533

Abstract. ***Background.*** *Candida albicans is the most frequent etiologic agent that causes opportunistic fungal infection called candidiasis, a disease whose systemic manifestation could prove fatal and whose incidence is increasing as a result of an expanding immunocompromised population. Here we review the role of interferon-gamma (IFN-γ) in host protection against invasive candidiasis. This study investigates the time- and sex-dependent variations in IFN-γ levels in C.albicans-infected rats, offering insights into the function of this cytokine in fungal immunity.* ***Materials and methods.*** *This study involved 100 rats, with 50 in the experimental group and 50 in the control group, each consisting of 25 males and 25 females. The experimental group received cyclosporine A (10 mg) 24 hours prior to the infection to suppress the immune response and facilitate C.albicans growth, whereas the control group was administered distilled water instead of C.albicans suspension. Following four days of infection, group 1 was anesthetized, and a blood sample was collected to measure IFN-γ levels. Group 2 was assessed at 8 days, group 3 at 12 days, group 4 at 16 days, and group 5 at 20 days, alongside the control group.* ***Results.*** *The present study demonstrated a significant increase ($p < 0.05$) in IL-10 concentration in both male and female rats infected with C.albicans compared to the control group. There was a significant increase in IFN-γ concentration in C.albicans-infected rats of both sexes, with a p value < 0.05, with progression of disease; the highest concentration was reached on the 12th day of the experiment and then decline. In contrast, no significant changes were observed in the control group over the same period.* ***Conclusions.*** *The research highlights the essential function of IFN-γ in the immune response to Candida albicans infections, observing that the absence of notable differences between male and female rats suggests that additional factors affect IFN-γ regulation. The necessity for additional research on the interactions between sex hormones and cytokines is underscored, offering insights into the sex- and time-dependent regulation of IFN-γ during infections, while also highlighting the need for clarification of observed discrepancies and their underlying mechanisms.*

Keywords: *IFN-γ; C.albicans; candidiasis; immune response; rats*

Introduction

Interferon-gamma (IFN-γ) is a critical cytokine in the host immune response to fungal infections, including those caused by *Candida albicans* [1]. As a key mediator of the Th1 immune response, IFN-γ enhances the antifungal activity of immune cells such as macrophages and neutrophils by promoting phagocytosis, the production of reactive oxygen species (ROS), and the expression of pro-inflammatory cytokines [2]. In rodent models, IFN-γ has been shown to play a pivotal role in controlling *C.albicans* infections, particularly during the acute phase of the immune response. However, the temporal dynamics of IFN-γ production during the early stages of infection remain an area of active investigation, as the immune response to *C.albicans* is highly regulated and varies depending on the stage of infection [3, 4].

Recent studies have demonstrated that IFN-γ levels do not significantly increase during the first four days of *C.albicans* infection in rats compared to control groups, suggesting a delayed or subdued early immune response [5].

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This initial phase may reflect the time required for the immune system to recognize the pathogen and mount an effective Th1 response. The lack of a significant increase in IFN-γ during this period could also be attributed to the immunosuppressive strategies employed by *C.albicans*, such as the modulation of host immune receptors and the production of virulence factors that dampen early pro-inflammatory responses [6]. Additionally, the early immune response to *C.albicans* is often characterized by the activation of innate immune mechanisms, such as the recruitment of neutrophils and the production of other cytokines like IL-6 and TNF-α, which may precede the upregulation of IFN-γ [7]. Understanding the delayed IFN-γ response in the early stages of *C.albicans* infection is crucial for elucidating the mechanisms of immune evasion employed by the fungus and for developing targeted immunotherapies [8, 9]. This study aims to explore the temporal dynamics of IFN-γ production in *C.albicans*-infected rats, with a focus on the first four days of infection, to provide insights into the early immune response and its implications for disease progression and control.

Materials and methods

Candida collection and identification

One hundred twenty stool samples were collected from children with diarrhea at Mohammed Al-Moussawi Teaching Hospital between October 2023 and February 2024. The samples were subsequently transferred daily to the Microbiology Laboratory in the Department of Life Sciences, College of Education for Pure Sciences. Diarrhea samples were cultured on Sabouraud dextrose agar with chloramphenicol and incubated at 37 °C for 24 to 48 hours. Following growth, the positive samples were re-cultured on chromogenic agar to differentiate between *Candida* species and were assessed for germ-tube formation.

Animal groups

Adult male and female albino rats (Rattus norvegicus) were obtained from the Laboratory Animal Breeding Center in Babylon Governorate, as outlined in the accompanying manual that facilitates the process. The animals were housed in the Animal House of Thi-Qar University College of Education for Pure Science, with weights ranging from 180 to 200 grams and an age of 8 weeks.

Fungal infection procedure in rats

In the study, a total of 100 mice were utilized, comprising 25 male and 25 female subjects injected with a fungal suspension, alongside a control group of 50 mice, also divided into 25 males and 25 females. These were organized into five groups, with each group consisting of five mice. The duration of the experiment was twenty days. Five rats per group were administered the immunosuppressant cyclosporin A (10 mg) once, 24 hours prior to the commencement of the experiment. The mice were administered a *C.albicans* fungal suspension (3×10^8 cells/ml) in a volume of 100 µl, equivalent to a concentration of 1 ml, orally using a specialized syringe, in a single instance, as a comparison to the standard McFarland solution. The distribution of animals was as follows:

— group 1. On the 4th day, the animals were anesthetized and blood was drawn directly from the heart;

— group 2. On the 8th day, the animals were anesthetized and blood was drawn directly from the heart;

— group 3. On the 12th day, the animals were anesthetized and blood was drawn directly from the heart;

— group 4. On the 16th day, the animals were anesthetized and blood was drawn directly from the heart;

— group 5. On the 20th day, the animals were anesthetized and blood was drawn directly from the heart.

Evaluation of IFN-γ

The IFN-γ was evaluated in serum of rats by using third generation ELISA technique.

Statistical analysis

The data of this study was statistically analyzed by using SPSS version 26, based in using one-way ANOVA, two-way ANOVA for mean variation, LSD, and Chi-square at p value < 0.05 [10]. The LSD value is used for determining the significant differences between means in the ANOVA test, where we subtract any two means from the table and compare the result of the subtraction with the LSD value. If the value of the subtraction is equal to or higher than the LSD value, it indicates a significant difference, while if it is less, it indicates that there is non-significant difference.

Results

Identification of Candida spp. in patients with diarrhea

The current study was showed the highest isolated *Candida* spp. in stool samples of patient was *C.albicans* 57 (78.1 %), then *C.glabrata* 11 (15.1 %), while the lowest isolated *Candida* spp. was *C.parapsilosis* 5 (6.8 %), also in control group showed highest isolated *Candida* spp. in stool samples of was *C.albicans* 8 (44.44 %), then *C.glabrata* 7 (38.89 %), while the lowest isolated *Candida* spp. was *C.parapsilosis* 2 (11.11 %), in addition the only one isolate of *C.tropicalis* in control group 1 (5.56 %) the study also noted a significant difference at p value < 0.05 between patients and control group, as in Fig. 1.

Distribution of Candida spp. according to sex

The current study was showed the highest isolated *C.albicans* in patient group was in the male group 39 (78.0 %), while the lowest in male group was *C.parapsilosis* 3 (6.00 %), in addition not *C.tropicalis* detected in patient group 0 (0.0 %), with regard control group noted the highest isolated *C.albicans* in female group and *C.glabrata* in male group 5 (50.0 %), while the lowest species was *C.tropicalis* in both female 1 (10.0 %), the study also noted a non-significant difference at p value < 0.05 in patients group and significant in control group, furthermore, a significant difference between patient and control group, as in Table 1.

Distribution of Candida spp. according to age groups

The current study was showed the highest isolated *Candida* spp. was in the first age groups *C.albicans* 32 (72.73 %), *C.glabrata* 8 (18.18 %), and *C.parapsilosis* 4 (9.09 %) while the lowest in male group 23 (31.51 %), while the lowest isolated *C.parapsilosis* in fourth age group 1 (12.5 %), while in control group the highest isolated was *C.albicans* in first age group 3 (75.0 %), then in third age group 3 (60.0 %), while the lowest isolated were *C.albicans* and *C.parapsilosis* in second age group 2 (28.57 %), the study also noted a significant difference within patient and within control, and between patient and control groups at p value < 0.05, as in Table 2.

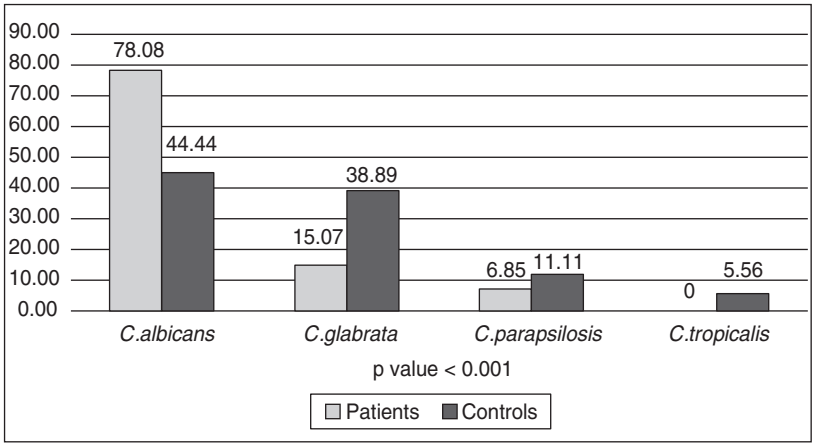

Figure 1. Identification of Candida spp. in patients with diarrhea and control group

Distribution of Candida spp. according to residency

The current study was showed the highest isolated *C.albicans* was in the countryside residence 48 (84.21 %), and in city residence 9 (56.25 %), while the lowest isolated *Candida* spp. was *C.parapsilosis* in both city and countryside residence 2 (12.5 %) and 3 (5.26 %), respectively, whereas in control group the study noted the highest isolated was *C.albicans* in countryside 4 (57.14 %), then *C.glabrata* in countryside 3 (42.86 %), while the lowest isolated was *C.tropicalis* 1 (9.09 %) in city residence, the study showed a significant difference at p value < 0.05 within patient

Table 1. Distribution of Candida spp. according to sex

Groups		Male		Female		p value
		N	%	N	%	
Patients	*C.albicans*	39	78.00	18	78.26	0.634
	C.glabrata	8	16.00	3	13.04	
	C.parapsilosis	3	6.00	2	8.70	
	C.tropicalis	0	0.00	0	0.00	
Controls	*C.albicans*	3	37.50	5	50.00	< 0.001
	C.glabrata	5	62.50	2	20.00	
	C.parapsilosis	0	0.00	2	20.00	
	C.tropicalis	0	0.00	1	10.00	

Notes: CalX² = 69.5; TabX² = 12.59; DF = 6; p value < 0.001.

Table 2. Distribution of Candida spp. according to age groups

Age groups, years		*C.albicans*		*C.glabrata*		*C.parapsilosis*		*C.tropicalis*		p value
		N	%	N	%	N	%	N	%	
Patients	< 1–2	32	72.73	8	18.18	4	9.09	0	0.00	< 0.001
	3–5	8	88.89	1	11.11	0	0.00	0	0.00	
	6–8	10	83.33	2	16.67	0	0.00	0	0.00	
	≥ 9	7	87.50	0	0.00	1	12.50	0	0.00	
Controls	< 1–2	3	75.00	1	25.00	0	0.00	0	0.00	< 0.001
	3–5	2	28.57	3	42.86	2	28.57	0	0.00	
	6–8	3	60.00	2	40.00	0	0.00	0	0.00	
	≥ 9	0	0.00	1	50.00	0	0.00	1	50.00	

Notes: CalX² = 302.6; TabX² = 19.68; DF = 11; p value < 0.001.

Table 3. Distribution of Candida spp. according to residency

Groups		City		Countryside		p value
		N	%	N	%	
Patients	*C.albicans*	9	56.25	48	84.21	< 0.001
	C.glabrata	5	31.25	6	10.53	
	C.parapsilosis	2	12.50	3	5.26	
	C.tropicalis	0	0.00	0	0.00	
Controls	*C.albicans*	4	36.36	4	57.14	< 0.001
	C.glabrata	4	36.36	3	42.86	
	C.parapsilosis	2	18.18	0	0.00	
	C.tropicalis	1	9.09	0	0.00	

Notes: CalX² = 43.6; TabX² = 12.59; DF = 6; p value < 0.001.

and within control and between patient and control, as in Table 3.

Evaluation of IFN-γ in rats according to sex

The analysis of serum IFN-γ levels revealed significantly elevated concentrations in the diseased group compared to the control group ($p < 0.01$). Male patients exhibited a mean IFN-γ level of 85.50 ± 21.10 pg/mL, while female patients had a slightly higher mean of 92.03 ± 18.60 pg/mL. In contrast, control males and females showed considerably lower levels, with means of 59.18 ± 4.77 pg/mL and 65.24 ± 7.32 pg/mL, respectively. Although both male and female patients demonstrated increased IFN-γ levels, there was no statistically significant difference between sexes within each group, as indicated by shared superscript letters. The least significant difference (LSD) value of 8.33 confirms the significance of differences observed between diseased and control groups. These findings suggest a potential role of elevated IFN-γ in the pathophysiology of the disease under investigation, as in Table 4.

Interaction between sex and time and it is effect of IFN-γ level

Longitudinal analysis of IFN-γ levels in patients and controls over a 20-day period revealed significant temporal and group-specific variations ($p < 0.01$). In both male and female patients, IFN-γ concentrations increased progressively from day 4 to day 12, peaking at 119.50 ± 5.35 pg/mL and 125.00 ± 3.58 pg/mL, respectively. This marked elevation was significantly higher than in the corresponding controls, where IFN-γ levels remained relatively stable throughout the study period. While patient values dropped slightly by day 20, they remained elevated compared to controls. Significant differences were observed between male and female patients at several time points, particularly on days 4 and 20, as indicated by the least significant difference (LSD) values. In contrast, no statistically significant differences were found between male and female controls at any time point ($p = 0.276$ and $p = 0.792$, respectively). The two-way ANOVA confirmed a significant interaction between time and group ($p < 0.01$, LSD = 9.03), emphasizing the dynamic and disease-specific modulation of IFN-γ. These findings suggest that IFN-γ could serve as a potential biomarker for disease progression and inflammatory status in affected patients, as in Table 5.

Table 4. Evaluation of IFN-γ (mean ± SD) in rats according to sex

Groups		IFN-γ
Patients	Male	85.50 ± 21.10[a]
	Female	92.03 ± 18.60[a]
Controls	Male	59.18 ± 4.77[b]
	Female	65.24 ± 7.32[b]
p value		< 0.01
LSD		8.33

Notes: [a] — the highest concentration, [b] — the second concentration.

Discussion

This finding of the present study was in line with previous studies, the study of Shankar et al. [11], that demonstrated the critical role of IFN-γ in the immune response to fungal infections, including candidiasis, and study of Glennon-Alty et al. [12], also recorded the IFN-γ is a key pro-inflammatory cytokine produced primarily by T helper 1 (Th1) cells and natural killer (NK) cells, and it plays a pivotal role in enhancing the antifungal activity of macrophages and neutrophils by promoting phagocytosis and the production of reactive oxygen species (ROS). The significant increase in IFN-γ levels in infected rats reflects the activation of a robust Th1-mediated immune response, which is essential for controlling *C.albicans* infections [13].

A non-significant difference in IFN-γ levels between male and female rats, both in the infected and control groups, is consistent with study of Abedini et al. [14], that had reported minimal sex-based differences in the production of IFN-γ during fungal infections. This suggests that the immune response to *C.albicans*, particularly the Th1

Table 5. Interaction between sex and time and it is effect of IFN-γ level, mean ± SD

Days	Patients		Controls		LSD
	Male	Female	Male	Female	
4	67.42 ± 8.85[c]	75.03 ± 7.86[c]	55.72 ± 3.76	64.47 ± 8.58	10.1
8	81.43 ± 8.21[b]	80.79 ± 4.97[c]	58.40 ± 4.58	61.83 ± 9.02	9.34
12	119.50 ± 5.35[a]	125.00 ± 3.58[a]	62.17 ± 6.92	67.37 ± 8.30	8.43
16	93.48 ± 14.10[b]	91.08 ± 6.00[b]	60.62 ± 3.17	67.00 ± 6.07	11.2
20	70.61 ± 8.58[c]	88.15 ± 6.48[b]	58.99 ± 3.70	65.55 ± 5.98	8.61
p value	< 0.01	< 0.01	0.276	0.792	p value < 0.01
LSD	12.4	7.86	Non-sig	Non-sig	

Notes: p value (LSD) < 0.01 (9.03); [a] — the highest concentration, [b] — the second concentration, and so on for the rest of the letters; also, the column that does not contain small letters did not record a significant difference.

response, may not be strongly influenced by sex hormones such as estrogen or testosterone. However, this finding contrasts with study of Harding and Heaton [15] that reported sex-based differences in cytokine production, with females often exhibiting stronger Th1 responses due to the immunomodulatory effects of estrogen. The discrepancy may be attributed to differences in experimental models, fungal load, or the timing of cytokine measurement, as the immune response can vary depending on the stage of infection [7].

The non-significant difference in IFN-γ levels between male and female rats in the control group further supports the idea that baseline levels of this cytokine are generally similar in the absence of infection. This is results was consistent with study of Dunn et al. [16] showing that sex-based differences in cytokine production are often more pronounced during active immune responses rather than at rest. However, previous study had reported subtle differences in baseline immune parameters between males and females, which could be influenced by genetic or environmental factors as reported by Bake et al. [17].

The results lie in the central role of IFN-γ in coordinating the immune response to *C.albicans*. The significant increase in IFN-γ in infected rats reflects the activation of a protective Th1 response, which is crucial for controlling fungal infections. The absence of sex-based differences in IFN-γ levels may be due to the dominant role of pathogen-associated molecular patterns (PAMPs) in driving the immune response, overshadowing the effects of sex hormones. Additionally, the timing of cytokine measurement in this study may have captured a phase of the immune response where sex-based differences are less pronounced.

The observed temporal pattern of IFN-γ levels in *Candida*-infected rats, characterized by an insignificant increase on the fourth day, a significant rise by the eighth day, a peak on the twelfth day, and a gradual decline by the sixteenth and twentieth days, reflects the dynamic nature of the immune response to fungal infections. IFN-γ, a critical Th1 cytokine, plays a pivotal role in activating macrophages and enhancing their antifungal activity through mechanisms such as phagocytosis and the production of reactive oxygen species as recorded by study of Ye et al. [18]. A similar study done by Pawar et al. [19], the initial insignificant increase on the fourth day likely represents the early phase of infection, where the immune system is still initiating its response, while the significant rise by the eighth day and peak on the twelfth day indicate the activation of a robust Th1-mediated immune response, essential for controlling *Candida* proliferation. The subsequent decline in IFN-γ levels by the sixteenth and twentieth days suggests a transition to immune regulation to prevent excessive inflammation and tissue damage, consistent with the resolution phase of the immune response as observed by study of Noori et al. [20]. Recent study performed by Wang et al. [21] had demonstrated that IFN-γ levels correlate with the severity and progression of fungal infections, with peak production occurring during the acute phase of infection. The gradual decrease in IFN-γ levels may also reflect the establishment of immune homeostasis or the suppression of Th1 responses by regulatory mechanisms, such as the induction of anti-inflammatory cytokines like IL-10 [22]. These findings underscore the importance of IFN-γ in the host defense against *Candida* and highlight the dynamic nature of the immune response over the course of infection. The value of chronobiological aspects in the functioning of kidneys and the expediency of continuing scientific and practical research in this direction of medical science were emphasized [23].

Conclusions

This study reveals a consistent temporal pattern of IFN-γ production in both mice and rats infected with *Candida* albicans, characterized by an insignificant increase on the fourth day, a significant rise by the eighth day, a peak on the twelfth day, and a gradual decline by the sixteenth and twentieth days of infection. This pattern reflects the dynamic immune response to *C.albicans*, beginning with a subdued IFN-γ response during early infection, followed by a robust Th1-mediated response to control fungal proliferation, and concluding with immune regulation to prevent excessive inflammation. These findings emphasize the critical

role of IFN-γ in host defense against *C.albicans* and provide insights into the temporal dynamics of cytokine production during fungal infections. Further research is needed to explore the mechanisms behind these changes and potential sex-based differences, which could guide the development of targeted immunotherapies for candidiasis.

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Received 01.06.2025
Revised 07.07.2025
Accepted 11.07.2025

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Conflicts of interests. Authors declare the absence of any conflicts of interests and own financial interest that might be construed to influence the results or interpretation of the manuscript.

Authors' contributions. Doaa Hazem Mohammed — conceptualization, data curation, investigation, methodology, project administration, resources, software, original draft, review & editing; Meethaq Sattar Abood, Ali Naeem Salman — conceptualization, data curation, investigation, methodology, project administration, original draft, review & editing.

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Імунна відповідь на інтерферон гамма у щурів, які були інфіковані *C.albicans*

Резюме. Актуальність. *Candida albicans* є найпоширенішим етіологічним агентом, що викликає опортуністичну грибкову інфекцію — кандидоз, системний перебіг якого може бути летальним. З огляду на збільшення кількості імунокомпрометованих осіб захворюваність на кандидоз зростає. У цьому дослідженні розглядається роль інтерферону гамма (IFN-γ) у захисті організму від інвазивного кандидозу. **Мета:** вивчити часові та статевозалежні зміни рівня IFN-γ у щурів, інфікованих *C.albicans*, щоб оцінити функціональну роль цього цитокіну в протигрибковому імунітеті. **Матеріали та методи.** У дослідження було залучено 100 щурів, розділених на експериментальну (n = 50) і контрольну (n = 50) групи, кожна з яких складалася з 25 самців та 25 самок. Тваринам експериментальної групи вводили циклоспорин А (10 мг) за 24 години до інфікування з метою пригнічення імунної відповіді та полегшення росту *C.albicans*. Контрольна група отримувала дистильовану воду. Вимірювання рівня IFN-γ проводили у п'яти часових точках: на 4-ту, 8-му, 12, 16 та 20-ту добу після інфікування. **Результати.** Отримані дані засвідчили вірогідне зростання концентрації IFN-γ ($p < 0,05$) у самців і самок щурів, інфікованих *C.albicans*, із максимальною концентрацією на 12-й день експерименту, після чого рівень цитокіну знижувався. У контрольній групі суттєвих змін IFN-γ протягом дослідження не зафіксовано. При цьому відмінностей в інтенсивності відповіді між статями не виявлено. **Висновки.** Отримані результати підтверджують важливу роль IFN-γ у протигрибковій імунній відповіді при інфікуванні *Candida albicans*. Відсутність виражених статевих відмінностей указує на можливу участь інших регуляторних факторів, зокрема гормональних. Необхідні подальші дослідження для з'ясування механізмів регуляції IFN-γ та його взаємодії зі статевими гормонами в контексті грибкових інфекцій.

Ключові слова: IFN-γ; *C.albicans*; кандидоз; імунна відповідь; щури