**Candida** Antigen Titer Elevation and Mortality in Burn Patients

Sebastian Jachec¹, Walter Perbix¹, Paul-Christian Fuchs¹, Rolf Lefering², Christian Weinand¹,³*

**ABSTRACT**

**BACKGROUND**

Mortality in burn patients has several contributing factors as sex, age, degree of burns, or inhalation injuries. Usefulness of Candida antigen (CAG) titer is still being under debate to predict mortality. This study assessed correlation between CAG titer and mortality in burn patients.

**METHODS**

From 1988 to 2011, 877 burn intensive care patients were evaluated for age, sex, total burn surface area (TBSA), multi organ failure (MOF), burn depth, escharotomy, fasciotomy, antibiotic use, co-morbidities, CAG titer and intubation.

**RESULTS**

From 870 admitted patients, 190 patients were not enrolled. Increasing age was correlated with a higher mortality. The abbreviated burn severity index (ABSI) score of the deceased was 4 points and the TBSA was 20% higher than the survivors. The correlation for age, intubation, TBSA, inhalation injury, MOF, CAG titer, antibiotic use and escharotomy was significant. An increasing mortality was noted with antibiotic use and a CAG titer of 1:8 and higher. CAG titer of 1:8 and higher had a sensitivity of 51.1% and specificity of 86.3% for mortality. Multivariate analysis confirmed high influence of older age, MOF, comorbidities, antibiotic use and CAG titer of 1:8 and higher on mortality. There was a significant correlation for sex, younger age and CAG titer.

**CONCLUSION**

CAG titers of 1:8 and higher might warrant beginning of antymycotic treatment in elderly patients with high TBSA to avoid increase in mortality.

**KEYWORDS**

Candida; Burn; Mortality; CAG titer

Please cite this paper as:

Jachec S, Perbix W, Fuchs PC, Lefering R, Weinand C. **Candida** Antigen Titer Elevation and Mortality in Burn Patients. World J Plast Surg 2019;8(1):18-24. doi: 10.29252/wjps.8.1.18.

**INTRODUCTION**

Mortality of burn injuries increases with higher total burned surface area and occurring infections.¹ Burn patients are susceptible to infections, because of the loss of the natural barrier and immuno-compromise. Burn size and defect are proportionate with odds of suspecting an infection.² As bacterial
infections can be detected with relative ease, suspicion of existing fungemia is found to be high in burn patients because of the existing immune suppression. Before the use of PCR or real-time PCR, CAG titer was widely used for detection of candidemia and showed its impact on finding the diagnosis. Nowadays, different methods have been developed. Current non-culture methods rely on a polymerase chain reaction (PCR) assay for candidemia.

Real-time PCR methods open up new perspectives for the early diagnosis of low candidemia, as an adjunct to blood culture. Real-time PCR has considerable advantages over conventional PCR in terms of sensitivity, handling, reduced contamination problems and has so far outperformed the CAG titer in diagnosing candidemia. Furthermore, it can be used to quantify the amount of template DNA and has been used to measure fungal loads. However, in none of the scores nowadays used fungal blood stream infection is being considered in calculating morbidity and mortality for the burn patient population. This is where measuring CAG titer might become a useful tool to predict increased mortality. Especially in the burn patients population who are susceptible to fungal blood stream infections, a swift and fast interference could be life-saving. Therefore, additional evaluation is mandatory. In our study, we evaluated the influence of the presence of CAG titer of 1:8 and higher on the mortality of a burn population of 870 patients, compared with other factors mentioned in literature.

**MATERIALS AND METHODS**

From January 1988 to December 2011, in 877 burn patients with thermic, electrical or chemical burns, admitted to our burn intensive care unit (BICU), CAG-titer was measured. Management was not changed significantly for patients during this time period. The inclusion criteria were sustained burn injury and burn intensive care needed, age over 14 years, no previous treatment outside our institution, ABSI data, and at least two CAG titers measured. Exclusion criteria were previous nystatin prophylaxis.

For evaluation several data were available, especially data on concomitant diseases of every patient, process of the burn injury and other sustained injuries, calculated abbreviated burn severity index (ABSI), all microbiological data of every patient, all CAG titers of all patients and data on catecholamine use, respiratory therapy and FiO₂, use of blood and blood products, and antibiotic and antymycotic therapy. Mortality of patients was the mortality of all the patients during and after burn intensive care treatment during the hospital stay. Patients who were discharged to other hospitals for further therapy were not included in the study.

In our hospital, the CAG titer was measured twice per week, using the latex agglutination test. When a patient showed increasing signs of infection in the laboratory (i.e. increasing white blood cell count, increasing c-reactive protein, increasing need of circulation supporting medication and increasing temperature) with MOF the titer was used for evaluation of the necessity of an antymycotic therapy.

A 1:2 CAG titer was ignored. If sepsis could not be explained otherwise and except for patients with pressure sores who usually showed CAG titers of 1:4 to 1:8, a titer of 1:8 often resulted in the use of antymycotic therapy. In patients with titers of 1:16 and higher, antymycotic therapy was always started. Antymycotics were chosen according to the antymycotic resistogram and during microbiology rounds, provided by the Department of Microbiology. In addition to antymycotic therapy, dressings were changed more often and topical antifungals were applied such as amphotericin B, or betaisodona and all

| Variable | Non-survival | Survival |
|----------|--------------|----------|
|          | n  | Mean  | SD  | n  | Mean  | SD  |
| Age      | 190 | 50.58 | 20.83 | 680 | 40.06 | 17.95 |
| ABSI     | 190 | 9.56  | 2.31  | 680 | 6.35  | 2.15  |
| TBSA     | 190 | 43.90%| 23.83 | 680 | 23.05%| 16.76 |
| 2a degree| 167 | 11.98%| 12.17 | 638 | 13.56%| 11.35 |
| 2b degree| 171 | 16.54%| 11.8  | 502 | 7.81% | 9.27  |
| 3rd degree| 170 | 19.92%| 13.6  | 372 | 7.60% | 9.89  |

Table 1: Burn patient population in this study.
Table 2: Univariate analysis of factors influencing mortality, Exitus=mortality.

| Variable                  | Non-survival n (%) | Chi-Square | Fischer Exact test |
|---------------------------|--------------------|------------|--------------------|
| Age [years] (Total)       |                    |            |                    |
| 0-19                      | 12 (13.3)          | 0.0001     | 0.001              |
| 20-39                     | 51 (15.1)          |            |                    |
| 40-59                     | 65 (23.1)          |            |                    |
| 60-79                     | 46 (36.8)          |            |                    |
| 80 and higher             | 16 (43.2)          |            |                    |
| Sex (total)               |                    | 0.094      | 0.1                |
| Male                      | 128 (20.4)         |            |                    |
| Female                    | 62 (25.6)          |            |                    |
| Intubation (total)        |                    | 0.0001     | 0.0001             |
| No                        | 7 (2.8)            |            |                    |
| Yes                       | 183 (29.6)         |            |                    |
| TBSA (total)              |                    | 0.0001     | 0.0001             |
| 0-9%                      | 11 (6.9)           |            |                    |
| 10-19%                    | 19 (8.4)           |            |                    |
| 20-29%                    | 33 (20.0)          |            |                    |
| 30-39%                    | 25 (24.0)          |            |                    |
| 40-49%                    | 27 (31.8)          |            |                    |
| 50-59%                    | 28 (51.9)          |            |                    |
| 60-69%                    | 17 (59.0)          |            |                    |
| 70-79%                    | 11 (50.0)          |            |                    |
| 80% and higher            | 19 (90.5)          |            |                    |
| MOF (total)               |                    | 0.0001     | 0.0001             |
| None                      | 18 (3.7)           |            |                    |
| 1 organ                   | 15 (11.8)          |            |                    |
| 2 or more organs          | 157 (61.8)         |            |                    |
| Inhalation injury (total) |                    | 0.0001     | 0.0001             |
| No                        | 62 (14.6)          |            |                    |
| Yes                       | 128 (28.7)         |            |                    |
| CAG titer (total)         |                    | 0.0001     | 0.0001             |
| 1:1                       | 27 (7.6)           |            |                    |
| 1:2                       | 29 (16.3)          |            |                    |
| 1:4                       | 37 (25.0)          |            |                    |
| 1:8                       | 55 (45.5)          |            |                    |
| 1:16                      | 42 (60.9)          |            |                    |
| Co-morbidities (total)    |                    | 0.003      | 0.004              |
| None                      | 61 (16.9)          |            |                    |
| 1 or more                 | 129 (25.3)         |            |                    |
| Antibiotic                |                    | 0.0001     | 0.0001             |
| No                        | 30 (12.6)          |            |                    |
| Yes                       | 160 (25.4)         |            |                    |
| Escharotomy               |                    | 0.0001     | 0.0001             |
| No                        | 97 (15.5)          |            |                    |
| Yes                       | 93 (38.0)          |            |                    |
| Fasciotomy                |                    | 0.001      | 0.001              |
| No                        | 164 (20.4)         |            |                    |
| Yes                       | 26 (39.4)          |            |                    |
catheters were exchanged.

The SPSS program (version 16.0, Chicago, IL, USA) was used for statistical analysis. For statistical evaluation univariate (age, sex, MOF, TBSA, burn depth, escharotomy, fasciotomy, antibiotic use, co-morbidities, and intubation), Chi-square and Fischer Exact test, multivariate model analysis, positive and negative predictive value, finite model analysis and the Nagelkerke and Cox and Snell R-square tests were used. The tested end point was non-survival. Differences were considered significant for a $p<0.05$.

RESULTS

870 patients were included into evaluation. When grouping into age groups, the first age group contended the highest number of patients (427 patients), the last groups, the lowest number of patients (37 patients). Increasing age showed higher mortality. Organ failure was grouped into no organ failure (489 patients), one organ failure (127 patients) and two or more organ failures (254 patients).

First patients were separated into non-survivors and survivors (Table 1), while 190 patients did not survive during the hospital stay (21.8%). The mean age of non-surviving patients was 50 years, and the survivors 40 years. The mean ABSI score was 4 points higher in the non-survivor group than in the survivor group, total TBSA was also 20% higher in the non-survivor group than in the survivors. Non-survivors had a higher percentage of 2nd and 3rd degree burns than survivors (Table 1).

When second univariate analysis was performed, the chosen endpoint was non-survival, and Chi-square and Fischer exact test were performed, variables tested were age groups in steps of 20 years, sex, intubation, TBSA in steps of 10% increased burned surface area, MOF, inhalation injury, CAG titer in doubling steps up to 1:16, co-morbidites, antibiotic use, escharotomy and fasciotomy. Co-morbidities and sex had the least influence on the outcome, CAG titer had a significance of 0.0001, comparable to the other tested variables (Table 2).

When the influence of antibiotic use on CAG titer was evaluated, use of antibiotic treatment led to a higher number of patients with CAG titer and there was no increase in CAG titer height with the use of antibiotic (Table 3). The next step was testing the sensitivity and specificity of CAG titer lower than 1:8 and 1:8 or higher for death and the positive and negative predictive value. The sensitivity was 51.1%, specificity

| Variable | n (%) | 1:1 | 1:2 | 1:4 | 1:8 | 1:16 | Total |
|----------|-------|-----|-----|-----|-----|------|-------|
| Antibiotic use | | | | | | | |
| No n (%) | 153 | 36 | 23 | 15 | 12 | 239 | (64) |
| Yes n (%) | 201 | 142 | 125 | 106 | 57 | 631 | (31.9) |
| Total n (%) | 354 | 178 | 148 | 121 | 69 | 870 | (40.7) |

| Variable | CAG-titer | | | |
|----------|-----------|-----|-----|-----|-----|-----|
| Non-survival | Below 1:8 | 1:8 or higher | Total |
| No n (%) | 587 | 93 | 680 | 86.3% | 13.7% | 100.0% |
| (% of non-survivors) | | | | | | |
| Yes n (%) | 93 | 97 | 190 | 48.9% | 51.1% | 100.0% |
| (% of non-survivors) | | | | | | |
| Total n (%) | 680 | 190 | 870 | 78.2% | 21.8% | 100.0% |
| (% of non-survivors) | | | | | | |
| (% of CAG-titer 1:8) | 100.0% | 100.0% | 100.0% | | | |
was 86.3%. The positive predictive value for a CAG titer of 1:8 and higher for impending non-
survival in our burn patients was 51.1%, while
the negative predictive value for CAG titer being
below 1:8 for survival was 86.3% (Table 4).

Multivariate analysis of the variables showed
a significance of \( p < 0.022 \) for CAG titer of 1:8
and higher. Intubation, no MOF or one organ
failure, inhalation injury, escharotomy and faschiotomy
were not found to be significant. The Nagelkerke
test for variance was \( r^2 = 0.611 \), showing a positive
correlation for the tested variables (Table 5).
In the calculated final element model those
variables were included that were significant in
the previous multivariate analysis.

Inhalation injury was also evaluated, because
this was a variable known to influence death as
outcome in burn population. Age group of 0-19

Table 5: Multivariate analysis, endpoint of the
evaluation is death, \( r^2 (\text{Nagelkerke}) = 0.611 \) for
variance.

| Variable     | \( P \) value |
|--------------|--------------|
| Age [years]  |              |
| 0–39         | 0.025        |
| 40–59        | 0.0001       |
| 60–79        | 0.0001       |
| 80 and higher| 0.0001       |
| Sex          | 0.012        |
| Intubation   | 0.298        |
| TBSA         | 0.0001       |
| MOF 1        | 0.056        |
| MOF 2 and more| 0.0001    |
| Inhalation injury | 0.172     |
| CAG titer 1.8 and higher | 0.022 |
| Co-morbidites | 0.0001     |
| Antibiotic   | 0.006        |
| Escharotomy  | 0.539        |
| Fasciotomy   | 0.154        |

Table 6: Finale element model with coefficient \( B \) for tested variables, standard variation of error (SE), Odds
ratio (OR), 95% confidence interval for OR and significance of variables (Sig). The CAG titer has comparable
weight like the sex or younger age for mortality.

| Variable           | \( B \) | \( SE \) | \( OR \) | 95% confidence Interval for OR | \( P \) value |
|--------------------|--------|--------|--------|-------------------------------|------------|
| Age 40-59          | 0.67   | 0.279  | 1.955  | 1.133-3.375                   | 0.016      |
| 60-79              | 2.069  | 0.358  | 7.915  | 3.921-15.978                  | 0.0001     |
| 80 and higher      | 2.212  | 0.558  | 9.130  | 3.060-27.239                  | 0.0001     |
| Sex                | 0.635  | 0.278  | 1.886  | 1.094-3.253                   | 0.022      |
| TBSA               | 0.042  | 0.006  | 1.043  | 1.031-1.056                   | 0.0001     |
| MOF 1              | 0.765  | 0.408  | 2.149  | 0.966-4.781                   | 0.061      |
| MOF 2 and more     | 3.122  | 0.318  | 22.698 | 12.180-42.297                 | 0.0001     |
| Inhalation injury  | 0.367  | 0.251  | 1.443  | 0.882-2.359                   | 0.144      |
| CAG titer 1:8 and higher | 0.570 | 0.247  | 1.769  | 1.091-2.869                   | 0.021      |

DISCUSSION

In this study, we evaluated the usefulness
and the weight of the CAG titer on prediction
of mortality in burn patients. Burn patients
are cited as being among the high risk groups
for invasive fungal infections.\(^8\) Burn wounds
provide an ideal port of entry for invasive
infection, while also inducing substantial
immune dysfunction.\(^9\) The risk increases with
burn size \(^10\) and the extent of burn body surface
has been correlated with immune suppression
and gastrointestinal mucosal atrophy, favoring
Candida translocation.\(^3\)

In our study, we found an increase of
mortality with age and burn size, but also an
increase of mortality with increased CAG titer
during the use of antibiotics. In a previous
study, we have shown a positive correlation
between the use of antibiotics, candidemia and
mortality.\(^11\) The importance of bacteremia and
prior antibacterial therapy as risk factors for
fungal invasive infections was also confirmed
by the study of Costa-de-Olivera, as half of the
patients had positive bacterial blood cultures
before the first fungemia episode and 93% of
them had received wide-spectrum antibacterial
drugs.\(^12\) This might explain the high coefficient
and 20-49 were combined for evaluation. CAG titer of 1:8 and higher had a significance of 0.021
with a coefficient of 1.7, as high as the tested variables sex and age group of 0-49 years. The highest weight in this model had MOF of two
or more organs with a coefficient of 3.1 and a
significance of 0.0001. The inhalation injury did
not have any influence on the outcome variable
of non-survival in our model (Table 6).
in our finale element model.

Data available from the Burn Unit of the University Hospital of Coimbra regarding fungal infections reported from 856 patients admitted from January 2003 to November 2007, 69 (8%) developed fungal infections. A higher mean age, a greater percentage of total burned body surface area, and a longer hospital stay in the burn unit were registered in patients who developed fungal infections.\textsuperscript{13,14} These findings are concordant with the results in our study.

According to Cheng \textit{et al.},\textsuperscript{15} the most important risk factors for \textit{C. albicans} candidemia are advanced age, invasive procedures associated with intensive care, and acute sepsis and, for non-albicans species, the most important risk factors were cancer chemotherapy in association with leucopenia and thrombocytopenia, the latter being a common finding among critical burn patients.

However, these factors and others like the CAG titer, which have critical weight in the assessment of intensive burn care patients, are not taken into account in current scores used for critically ill or burn patient population such as the ABSI score, the Belgian score or the Flames score.\textsuperscript{1,16,17} These burn scores included several factors such as sex, age, TBSA, 3rd degree burns, inhalation injury, heart rate, arterial pH, mean arterial pressure, creatinine, hematocrit, white blood cell count, Glasgow coma scale, rectal temperature and AaDO2. We therefore calculated, based on the majority of these burn score factors, the sensitivity and specificity of the CAG titer to predict mortality.

According to a previous study,\textsuperscript{4} PCR detection of fungal DNA had a sensitivity of 72.1%, a specificity of 91.2%, and a negative predictive value of 93.2%, when compared with blood culture. For patients with known predisposing factors for candidemia, who have negative blood cultures, a positive PCR result from blood may represent a reliable evidence of invasive candidosis, thus providing a rationale for the initiation of targeted antifungal therapy.\textsuperscript{4} In our study, we calculated for the CAG titer a sensitivity of 51.1%, a specificity of 83.6% and a negative predictive value of 86.3%.

However, although considerable efforts are being developed along the last couple of years to validate non-culture methods and molecular assays as diagnostic tools for fungal blood stream infections, the lack of standardization and/or reduced specificity and sensitivity still precludes its routine diagnostic use.\textsuperscript{6} Additionally, in clinical settings, where diagnosis of candidemia leans heavily on the use of real-time PCR or PCR while these tests are not available, clinical importance of CAG titer should not be underestimated.\textsuperscript{7}

The fast and reliable specification and susceptibility testing are important tests to be performed for all fungal isolates, including \textit{Candida} obtained from sterile sites, from urine of burn patients in ICU, and from wounds. In fact, a progressive increase in colonization almost invariably predicts the development of invasive candidosis.\textsuperscript{18,19} An invasive candidosis might lead to a life threatening candidemia, especially in immune-compromised patients.\textsuperscript{7} Here, a CAG titer of 1:8 and higher might be a valuable predictor to an increased risk for mortality in burn patients. However, an increasing CAG titer by itself has also been reported a Dumping–phenomenon in a previous study.\textsuperscript{19} It might be therefore necessary to take all clinical variables of the patient into account. The CAG titer might be considered a useful adjunct in the assessment of mortality in burn patients.

**ACKNOWLEDGEMENT**

This work was made possible by departmental funds only.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

**REFERENCES**

1. Saaq M, Ashraf B. Epidemiology and outcome of self-inflicted burns at pakistan institute of medical sciences, islamabad. World J Plast Surg 2014;3:107-14.
2. Saaq M, Ahmad S, Zaib MS. Burn wound infections and antibiotic susceptibility patterns at pakistan institute of medical sciences, islamabad, pakistan. World J Plast Surg 2015;4:9-15.
3. Moon P, Jithendran N. Invasive Fungal Infection with Absidia Corymbifera in Immunocompetent Patient with Electrical Scalp Burn. World J Plast Surg 2018;7:249-52.
4. Moreira-Oliveira MS, Mikami Y, Miyaji M, Imai T, Schreiber AZ, Moretti ML. Diagnosis
of candidemia by polymerase chain reaction and blood culture: prospective study in a high-risk population and identification of variables associated with development of candidemia. *Eur J Clin Microbiol Infect Dis* 2005;24:721-6. doi: 10.1007/s10096-005-0041-7.

5 Maaroufi Y, De Bruyne JM, Duchateau V, Georgala A, Crokaert F. Early detection and identification of commonly encountered Candida species from simulated blood cultures by using a real-time PCR-based assay. *J Mol Diagn* 2004;6:108-14. doi: 10.1016/S1525-1578(10)60498-9.

6 Maaroufi Y, Ahariz N, Husson M, Crokaert F. Comparison of different methods of isolation of DNA of commonly encountered Candida species and its quantitation by using a real-time PCR-based assay. *J Clin Microbiol* 2004;42:3159-63. doi: 10.1128/JCM.42.7.3159-3163.2004.

7 Sonmez A, Eksi F, Pehlivan M, Haydaroglu Sahin H. Investigating the presence of fungal agents in febrile neutropenic patients using different microbiological, serological, and molecular methods. *Bosn J Basic Med Sci* 2015;15:40-7. doi: 10.17305/bjbms.2015.409.

8 Trautwein-Weidner K, Gladiator A, Kirchner FR, Becattini S, Rulicke T, Sallusto F, LeibundGut-Landmann S. Antigen-Specific Th17 Cells Are Primed by Distinct and Complementary Dendritic Cell Subsets in Oropharyngeal Candidiasis. *PLoS Pathog* 2015;11:e1005164. doi: 10.1371/journal.ppat.1005164.

9 Ballard J, Edelman L, Saffe J, Sheridan R, Kagan R, Bracco D, Cancio L, Cairns B, Baker R, Fillari P, Wibbenmeyer L, Voight D, Palmieri T, Greenhalgh D, Kemalyan N, Caruso D, Multicenter Trials Group ABA. Positive fungal cultures in burn patients: a multicenter review. *J Burn Care Res* 2008;29:213-21. doi: 10.1097/BCR.0b013e31815f6ecb.

10 Still JM, Jr., Belcher K, Law EJ. Management of candida septicaemia in a regional burn unit. *Burns* 1995;21:594-6. doi: 10.1016/0305-4179(95)00069-n.

11 Jachec S, Perbix W, Lefering R, Diaz C, Spilker G, Weinand C. Candida-Antigen-Titer (CAG-Titer) for Detection and Early Treatment of Impending Candidemia. *J Med Health Sci* 2015;4:1-6.

12 Costa-de-Oliveira S, Pina-Vaz C, Mendonca D, Goncalves Rodrigues A. A first Portuguese epidemiological survey of fungaemia in a university hospital. *Eur J Clin Microbiol Infect Dis* 2008;27:367-74. doi: 10.1007/s10096-007-0448-4.

13 Caetano M, Ramos S, Abreu J. Fungal infections at a Coimbra burns unit: 2003–2007. Abstract book [CD-ROM]. Presented at: 18th ECCMID. Abstract number R2459.

14 Pedrosa AF, Rodrigues AG. Candidemia in burn patients: figures and facts. *J Trauma* 2011;70:498-506. doi: 10.1097/TA.0b013e3181f2d4fb.

15 Cheng MF, Yang YL, Yao TJ, Lin CY, Liu JS, Tang RB, Yu KW, Fan YH, Hsieh KS, Ho M, Lo HJ. Risk factors for fatal candidemia caused by Candida albicans and non-albicans Candida species. *BMC Infect Dis* 2005;5:22. doi: 10.1186/1471-2334-5-22.

16 Belgian Outcome in Burn Injury Study G. Development and validation of a model for prediction of mortality in patients with acute burn injury. *Br J Surg* 2009;96:111-7. doi: 10.1002/bjs.6329.

17 Tobiasen J, Hiebert JM, Edlich RF. The abbreviated burn severity index. *Ann Emerg Med* 1982;11:260-2. doi: 10.1016/s0196-0644(82)80096-6.

18 Pittet D, Monod M, Suter PM, Frenk E, Auckenthaler R. Candida colonization and subsequent infections in critically ill surgical patients. *Ann Surg* 1994;220:751-8. doi: 10.1097/00000658-199412000-00008.

19 Eggimann P, Pittet D. Candida colonization index in the management of critically ill patients. In: Vincent JL, ed. Intensive Care Medicine. Annual Update 2006. New York: Springer New York; 2006; pp. 604-2.