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## Nephrology

### Original Article

#### Intermittent fasting in Ramadan in patients on maintenance hemodialysis: Relation to malnutrition, inflammation, body composition and quality of life

Mohammed Kamal Nassar · Eman Nagy · Ghada El-Kannishy · Nagy Sayed-Ahmed - 1

## Periodontology

### Review

#### A Prevailing Approach in Periodontal Plastic Surgery: Tunnel Technique

Hikmat Bakhishov - 6

## Psychology and Psychiatry

### Original Article

#### Missed opportunities in the assessment and management of suicidal youth in a developing country

Naseema Vawda · Enver Karim - 13

## Biochemistry

### Original Article

#### Comparison Between Serum Procalcitonin Measurement Using Rapid Test Fluorescent Immunoassay (FIA) Method and Electrochemiluminescence Immunoassay (ECLIA) Method In Sepsis Detection

I Putu Adi Santosa · Dian Luminto · Anik Widijanti · Catur Suci Sutrisnani - 18

## Transplantology

### Review

#### Guidelines for transplant patients during the COVID-19 pandemic

Nuru Bayramov · Elvin Isazade · Ruslan Mammedov · Anar Namazov - 23

## Pediatrics

### Case Report

#### Hemolytic Uremic Syndrome Still Confuses Minds: A Case With All Three Components of the Triad

Fazil Rajabov · Erkin Rahimov · Zaur Akhmadov - 25

## DOI

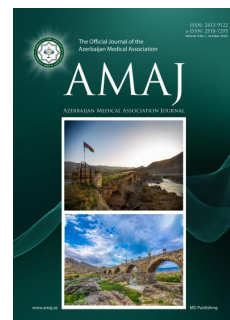
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## The Cover: Khudafarin bridges

Two Khudafarin bridges (Azerbaijani: Xudafərin körpüləri) connecting the northern and southern banks of the Aras River are magnificent historical architectural monuments, which are located on the border of Azerbaijan and Iran. Khudafarin bridges are the most significant examples of the national architecture of Azerbaijan. The magnificent historical architectural monuments with the 11-arches and 15-arches were built on natural large boulders and rocks in the Khudafarin canyon at ancient times (7th-13th centuries). Connecting the northern and southern banks of the Aras River, bridges served as a major junction of the historical Great Silk Road. Located on the border of Azerbaijan (Jabrayil Region) and Iran (East Azerbaijan Province), Khudafarin bridges gained regional and international value. Taking into account the exceptional universal value, high architectural and engineering solutions Azerbaijan intends to take measures to include the Khudafarin Bridges in the UNESCO World Heritage List.

From 1993 to October 2020, Jabrayil district was occupied by Armenian forces that abandoned these bridges. Since October 18th, the Azerbaijani forces took back control of the region and of these historical and symbolic monuments.

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# Intermittent fasting in Ramadan in patients on maintenance hemodialysis: Relation to malnutrition, inflammation, body composition and quality of life

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**Objective:** Many previous studies suggest that intermittent fasting has beneficial effects on health. Fasting during the month of Ramadan can be considered as a model of intermittent fasting among Muslims. The present study aimed to assess the effect of Ramadan fasting on quality of life (QOL) and body composition in hemodialysis (HD) patients.

**Material & methods:** Sixty-eight patients on maintenance HD for more than six months in Mansoura Nephrology and Dialysis Unit (MNDU) were included in this prospective observational study. Patients' nutritional status was assessed by malnutrition inflammation score (MIS). Anthropometric measurements including body weight, height, mid arm circumference (MAC), and triceps skin fold thickness (TSF) were measured. Body composition was assessed by bioelectrical impedance. Quality of life was assessed by using the Kidney Disease Quality of Life-36 (KDQOL-36™). Assessment of all patients was carried out before the start of Ramadan and repeated 3 weeks after Ramadan in patients who fasted more than 14 days.

**Results:** Forty-five patients (66%) fasted more than 14 days during the month of Ramadan. Insignificant weight gain was observed in patients who fasted after Ramadan. Interestingly, visceral fat was significantly reduced after Ramadan ( $p < 0.0001$ ). MIS score improved with lower score estimated after Ramadan; however, the difference was insignificant ( $p = 0.059$ ). Also, mental health component of QOL improved after Ramadan.

**Conclusion:** Fasting in Ramadan in HD patients was associated improvement of the metabolic profile evident by decrease in visceral fat. Ramadan fasting had a positive effect on mental wellbeing. The effect of intermittent fasting on inflammation and nutritional parameters in patients on maintenance hemodialysis needs further investigations.

**Keywords:** Ramadan fasting, nutrition, inflammation, quality of life, hemodialysis, chronic kidney disease.

## Introduction

Intermittent fasting can be considered as an alternative to daily caloric restriction for individuals who are interested in improving body composition and overall health in addition to reduce body weight and body fat. [1]

Ramadan is the 9th month of the Islamic lunar calendar during which all healthy adult Muslims are required to abstain from eating any food and drinks from dawn to sunset, with exclusions of severely ill peo-

ple, menstruating females, pre-pubertal children, and travelers. The fasting hours can vary from 12 to 17 hours, relying on the seasonal and regional features. [2] Fasting during the month of Ramadan can be considered as a model of intermittent fasting among Muslims.

In the randomized crossover trial of intermittent fasting aiming to examine the effect of changing eating frequency without caloric restriction subjects were allowed to eat only for 4 hours in the evening. Stote

and colleagues reported that body weight and fat mass were reduced with non-significant increase in fat-free mass. The authors concluded that intermittent fasting protocol could lead to a concomitant decrease in fat mass and increase in fat-free mass, it would be a beneficial and appealing dietary strategy to many individuals. [3] The impact of Ramadan fasting on physiological and biomedical markers among healthy people has been broadly studied. Research evidence suggests that Ramadan fasting is tolerable and safe for healthy adults. [4-7]

Although Islam allows ill people and those with significant health problems not to fast, [8] many patients still desire to fast during Ramadan. Several studies have examined the effect of Ramadan fasting on several markers in patients with kidney diseases. Ramadan fasting was not associated with significant adverse effects in kidney transplant patients after one year of kidney transplantation, [9] or patients with recurrent urinary stone formation. [10] However, research findings on the safety of Ramadan fasting by patients with chronic kidney disease (CKD) on maintenance hemodialysis (HD) are mixed and controversial. [11, 12] Some studies have reported that Ramadan fasting was associated with significant changes in clinical and biomedical markers, such as fluid overload and hyperkalemia, but with no significant complications requiring hospitalization. [13, 14] Other studies found no clinically important variations in medical parameters in HD patients during Ramadan fasting. [15, 16]

End stage renal disease (ESRD) is a chronic disease that exerts a great negative impact on patients' health-related quality of life (QOL) mainly due to the accompanied impairment or to the imposed limitations in almost all domains of their daily lives. [17]

To the best of our knowledge, no studies had specifically examined the effect of fasting Ramadan, as a religious form of intermittent fasting, on nutritional and body composition parameters as well as QOL in HD patients. Therefore, this study was carried out to explore the effects of Ramadan fasting on these parameters in this special category of patients. It is hypothesized that fasting in Ramadan may have beneficial effects on nutritional and inflammatory parameters of HD patients.

## Material & Methods

This prospective observational study was conducted in our unit. The study was performed in Ramadan 1440 Hijri when the fasting hours ranged from 15 to 16 hours. All patients on maintenance HD for more than six months in the unit were observed for their fasting pattern without interference from the authors and without any instruction about caloric restriction. Patients who were pregnant or lactating, or had an active infection, malignancy or evidence of heart or liver disease were excluded from the study. All patients were subjected to full history taking, including hemodialysis duration, educational and occupational status. All assessments were carried out before the start of Ramadan and repeated 3 weeks after Ramadan in patients who fasted more than 14 days.

**Anthropometric measurements:** Post dialysis body weight (kg), and height (m) of all patients were measured and body mass index (BMI) was calculated. Mid upper arm circumference (MAC) was measured in centimeters (cm) twice using a flexible, inelastic measuring tape in the non-arteriovenous fistula arm, just at the mid-point of upper arm (i.e. between the acromion process of scapula and the olecranon process of ulna), in sitting position, and the average was recorded. [18] Triceps skin fold (TSF) thickness was measured in millimeters (mm) twice using skin fold caliper at the mid-point of back of upper arm, as mentioned above, by taking a fold of skin away from muscle while the patient standing upright, with arms hanging down loosely [19] then mid arm muscle circumference (MAMC) was calculated in cm by the formula:  $MAMC = MAC - ([TSF/10] \times \pi)$ . [18]

**Body composition measurement:** Bioelectrical impedance analysis (BIA) was carried out using Tanita body composition monitor BC-601FS (TANITA Corporation, Maeno-Cho, Itabashi-ku, Tokyo, Japan) after a hemodialysis session to obtain the percentage of total body water (TBW) and total body fat, as well as the fat free mass in Kg and visceral fat rating.

**Malnutrition inflammation score (MIS):** MIS is composed of ten components, categorized in four sections—medical history (change in dry weight, dietary intake, gastrointestinal symptoms, functional capacity, and comorbidity), physical examination, body mass index (BMI), and laboratory values. Each MIS component has four levels of severity from 0 (normal) to 3 (very severe). The sum of all 10 components results in an overall score ranging from 0 (normal) to 30 (severely malnourished). [20]

**Assessment of QOL:** Assessment of QOL was performed by using the Kidney Disease Quality of Life-36 (KDQOL-36™). The first version contained the Medical Outcomes Study 36 (MOS SF-36) as a generic chronic disease core, in addition to items related to patients with kidney disease. It had 36 questions; mental health composite (MHC) and physical health composite (PHC), burden of kidney disease, symptom/problem list and effect of kidney disease components of QOL were obtained from questions 1-12, 1-12, 13-16, 17-28 and 29-36 respectively. The average scores of these five components of KDQOL-36 were ranged from 0-100 with higher scores indicating better health-related QOL. [21]

**Statistical analysis:** The collected data were recorded, coded, tabulated and analyzed for statistical purposes by utilizing the Statistical Package for Social Science (SPSS) version 25 for Windows on personal computers. Qualitative variables were described as percentages and numbers, and after testing normality by the Kolmogorov-Smirnov test, normally distributed quantitative variables were described as means [ $\pm$  standard deviation (SD)], while non-parametric variables were reported as medians (interquartile range; IQR). For paired comparison, paired t test and Wilcoxon test were used for parametric and non-parametric variables respectively. P value  $\leq 0.05$  was statistically significant.

## Results

Forty-five patients (66%) of HD patients fasted more than 14 days during the month of Ramadan. Demographic and clinical data of the patients are shown in table 1. The mean age of the patients was  $47.33 \pm 14.86$  years with a median HD duration of 35 months. The mean fasting days was 17.84 with SD 4.36. More than three quarters (84.4%) of the patients were hypertensive. One third of patients lived in urban regions, while the other two thirds lived in rural regions. Only 8 patients were employed, and 35 patients were educated.

Patients who fasted Ramadan were overweight (BMI:  $28.7 \pm 6.06$  kg/m<sup>2</sup>) with a mean total fat percentage of 29.4%. The median score of MIS was 3. Non-significant increase in BMI was observed after Ramadan (*p* value 0.073). MAC, TSE, MAMC, FFM, and TBW percentage were not affected by Ramadan fasting. Both total fat percentage and visceral fat rating were reduced after Ramadan fasting, but this reduction was significant for latter only (*p* <0.0001). The MIS value was not affected by fasting (Table 2).

Regarding QOL, the MHC domain of QOL improved after Ramadan (*p*=0.057). However, none of the five domains of health related QOL showed significant change in the HD patients after Ramadan fasting (Table 2).

## Discussion

Intermittent fasting is a broad term that encompasses a variety of programs that manipulate the timing of eating occasions by utilizing short-term fasts in order to improve body compo-

**Table 1.** Demographic and medical history of fasted group.

| Parameter                   | Fasting group n=45 (%)  |
|-----------------------------|-------------------------|
| Age of at diagnosis         | $47.33 \pm 14.86$ years |
| Gender                      |                         |
| Male                        | 21 (46.7%)              |
| Female                      | 24 (53.3%)              |
| Duration of HD (months)     | 35 (14.5–74.5)          |
| Fasting days, mean $\pm$ SD | $17.84 \pm 4.36$        |
| Diabetes milletus           |                         |
| Yes                         | 5 (11.1%)               |
| No                          | 40 (88.9%)              |
| Hypertension                |                         |
| Yes                         | 38 (84.4%)              |
| No                          | 7 (15.6%)               |
| Residence                   |                         |
| Urban                       | 15 (33.3%)              |
| Rural                       | 30 (66.7%)              |
| Occupation                  |                         |
| Employed                    | 8 (17.8%)               |
| Unemployed                  | 37 (82.2%)              |
| Education                   |                         |
| Illiterate                  | 10 (22.2%)              |
| Educated                    | 35 (77.8%)              |
| Marital status              |                         |
| Married                     | 30 (66.7%)              |
| Unmarried                   | 15 (33.3%)              |

**Table 2.** Anthropometric measures and QOL of fasting group before and after Ramadan fasting.

| Parameter   | Before Ramadan    | After Ramadan    | P value |
|---|-------------------|------------------|---------|
| Body mass index (Kg/m <sup>2</sup> ), mean $\pm$ SD | $28.7 \pm 6.06$   | $29.04 \pm 6.09$ | 0.073   |
| Mid-arm circumference (cm), mean $\pm$ SD           | $30.9 \pm 5.25$   | $30.8 \pm 5.33$  | 0.69    |
| Triceps skin fold thickness (mm), median (Q1-Q3)    | 14 (12–21.5)      | 14 (10–20)       | 0.41    |
| Mid-arm muscle circumference (cm), mean $\pm$ SD    | $25.5 \pm 3.08$   | $25.6 \pm 3.11$  | 0.84    |
| Total fat percentage, mean $\pm$ SD                 | $29.4 \pm 10.96$  | $28.2 \pm 10.64$ | 0.36    |
| Fat free mass (kg), mean $\pm$ SD                   | $51.48 \pm 9.2$   | $52.48 \pm 9.4$  | 0.228   |
| Total body water percentage, mean $\pm$ SD          | $51.8 \pm 8.74$   | $52.7 \pm 8.65$  | 0.45    |
| Visceral fat rating, median (Q1-Q3)                 | 7 (4–10)          | 4 (2–8.5)        | <0.0001 |
| Malnutrition inflammation score, median (Q1-Q3)     | 3 (2–5.5)         | 3 (2–5)          | 0.059   |
| Symptom/problem list, median (Q1-Q3)                | 77.1 (70.8–89.5)  | 81.2 (69.7–91.6) | 0.800   |
| Effect of kidney disease, median (Q1-Q3)            | 75 (56.2–89.0)    | 81.2 (64–90.6)   | 0.150   |
| Burden of kidney disease, median (Q1-Q3)            | 50 (28.1–75)      | 50 (25–75)       | 0.180   |
| Physical health composite, median (Q1-Q3)           | 41 (30.7–45.9)    | 36 (29.3–48)     | 0.490   |
| Mental health composite, median (Q1-Q3)             | 47.25 (39.5–57.5) | 51.7 (43.6–60.8) | 0.057   |

sition and overall health. [1] Time-restricted feeding protocols involve adhering to a daily routine that requires fasting for a certain number of hours and feeding for the remaining hours in a 24-hour period. [22] Many previous studies suggest that intermittent fasting has beneficial effects on health. [23-25] Ramadan fasting is one of the five pillars of Islam and is obligatory for all healthy adults. Although chronic HD patients are exempt from Ramadan fasting, many of them insist to fast. Safety of Ramadan fasting in chronic HD patients is debatable. Evidence is lacking as regard the effect of Ramadan fasting as a model of intermittent fasting on body composition and nutritional parameters HD patients. Therefore, this study aimed to assess the effect of Ramadan fasting on nutritional parameters and body composition as well as QOL in a group of HD patients in a single HD center.

Forty-five patients (66%), out of 68 patients, in our center fasted more than 14 days in Ramadan. The Frequency of fasting Ramadan in HD patients reported in previous studies is variable. Adnan et al [16] stated that 89% of patients in three HD centers in Malaysia fasted in Ramadan. In Pakistan, the frequency of fasting in Ramadan was 13.5% as reported by Imtiaz and his coworkers. [15] In another study conducted in Saudi Arabia, 64.1% out of the included 635 HD patients fasted. [26] In a recent study conducted in Egypt, 46.96% of the included 2055 Muslim HD population in 27 HD centers fasted at least few days of Ramadan. [27] This difference may be due to different demographic characteristics of the investigated HD patients. Furthermore, Megahed et al, stated that the absence of specific guidelines advocating or prohibiting fasting in this special situation makes fasting in HD population an individual decision that mirrors patients' own motivation and capability. [27]

Mean patients BMI in the current study was  $28.7 \pm 6.06$  kg/m<sup>2</sup>. This may explain the high frequency of fasting in our HD center. Although fasting in Ramadan is expected to be associated with weight loss due to decrease in meals frequency and caloric intake, the BMI was insignificantly increased after Ramadan in the studied HD patients. Al Wakeel, Imtiaz et al and Adnan et al studies also reported non-significant change in dry body weight after Ramadan fasting. [13, 15, 16]

Although BMI is considered as a key nutritional assessment tool in patients with CKD, [28] it cannot represent the real nutritional status in HD patients. [29] Skinfold thickness and percentage of body fat have been reasonably well validated against established gold standards and provide estimates of fat mass superior to BMI in CKD patients. [30] In the current study, TSF as well as total fat percentage showed non-significant change after Ramadan fasting. Interestingly, visceral fat rating decreased significantly after Ramadan fasting.

Visceral adipose tissue is found mainly in the mesentery and omentum and has been described to be more metabolically active, more sensitive to lipolysis, and more insulin-resistant compared to subcutaneous fat. Further, visceral adipose tissue is more cellular, vascular, and innervated, and it contains a larger number of inflammatory and immune cells as compared to subcutaneous fat. Also, it has a greater capacity than subcutaneous fat to generate free fatty acids and to take up glucose. [31-37] Epidemiologic and clinical studies over the past 30 years have

clearly demonstrated a strong link between visceral fat and the development of clinical syndrome characterized by atherogenic dyslipidemia, hyperinsulinemia/glucose intolerance, hypertension, atherosclerosis, and adverse cardiac remodeling/heart failure. [38] Abdominal obesity underlies a high risk of all-cause and cardiovascular mortality in patients with end stage renal disease. [39] This decrease in visceral fat rating observed after fasting in the studied HD patients denotes improvement in metabolic profile and suggest a possible protection of intermittent fasting from cardiovascular diseases in hemodialysis.

Degaldo and his coworkers in 2017 performed linear regression analyses to examine the extent to which proxies of visceral and subcutaneous fat were associated with inflammation, nutrition, and adiposity-related hormones in HD patients. They concluded that proxies of visceral and subcutaneous fat appear to have opposing associations with biomarkers of inflammation and nutrition. Subcutaneous fat may be an indicator of nutritional status, and visceral fat, an indicator of inflammation. [40] According to the results of the current study, MIS showed non-significant decrease after fasting ( $p=0.056$ ). Although it is difficult to draw a clear conclusion about the effect of short-term intermittent fasting in HD patient on inflammation, it is evident that Ramadan fasting does not adversely affect nutritional status in the studied cohort. More investigations are needed to explore the extent to which visceral fat loss after intermittent fasting affect markers of nutrition and inflammation in patients on HD.

Fasting was not associated with muscle mass loss. Anthropometric measures (MAC and MAMC) as well as fat free mass showed no significant change after Ramadan fasting. The preservation of muscle mass is very important in HD patients as it is related to lower all-cause mortality, [41] and improved muscle function. [42] In the current study, fasting was not associated with muscle mass loss. MAC and MAMC as well as fat free mass did not change significantly after Ramadan fasting; a finding that matches the results of a Malaysian multicenter, prospective observational study of 87 HD patients. However, they observed improved muscle function, assessed by hand grip strength (HGS). They explained that the improvement in HGS, despite no change in muscle mass, may be due to the increased physical activity induced by performing extended hours of praying after the sunset. [43]

Fasting the month of Ramadan is a very special type of worship associated with many spiritual benefits. Mental health composite of QOL in the studied HD patients improved after Ramadan ( $p=0.057$ ). The positive outcome of Ramadan fasting on mental wellbeing may be related to the fact that fasting discipline soul and moral behavior. During the blessed month, there is increase sense of gratitude and social relationships.

Finally, we admit that this study has some limitations; namely, the small sample size and the single-center nature of the study. Furthermore, it would be better to assess more biochemical, inflammatory, and nutritional parameters. However, detailed assessment of the effect of Ramadan fasting on the body composition in HD patients is considered one of the strengths of this study.



## Conclusion

In conclusion, fasting Ramadan in a cohort of Egyptian HD patients was not associated with detrimental effects on the studied nutritional, inflammatory and anthropometric parameters. Moreover, it may be associated with an advantageous effect on the metabolic profile. However, more studies including a larger number of HD patients from multiple center and assessing more biochemical, inflammatory, and nutritional biomarkers are needed.

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# A Prevailing Approach in Periodontal Plastic Surgery: Tunnel Technique

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**Objective:** To review the current concepts for the treatment of multiple gingival recessions and present tunnel technique in periodontal plastic surgery.

**Data & sources:** The literature was searched for review and original research articles and case series relating tunnel technique on the treatment of multiple gingival recessions.

**Conclusion:** Tunnel technique provides unique treatment option especially for the multiple gingival recessions. Despite the few limitations, accumulating data favours tunnel technique resulted in remarkable outcomes along with better final aesthetics.

**Keywords:** gingival recessions, periodontal plastic surgery, tunnel technique, connective tissue graft.

## Anatomy of the gingiva

Clinically, the gingiva may be regarded as a combination of epithelial and connective tissues that, forms a collar of masticatory mucosa around the teeth of the complete deciduous or permanent dentition and is attached to both teeth and the alveolar process. It covers the alveolar crest, the interdental septa, and the coronal portion of the alveolar process to the mucogingival junction. The tissues of the gingiva have classically been subdivided into several topographical portions: free, attached and interdental gingiva. Likewise, the term keratinized gingiva is redundant, as the oral surface of the gingiva, by definition, is lined by keratinizing epithelium. In fact, the gingiva is an anatomical and functional unit with variations in shape, contour and clinical topography that result in part from tissue adaptation to the specific location around teeth. Sufficient amount of keratinized gingiva around teeth and resulting immobility of marginal tissues hinder bacterial invasion of gingival sulcus [1]. Presence of enough keratinized gingiva improves soft tissue thickness and decrease risk for mucosal recessions around dental implants [2].

## Gingival recession

Gingival recessions (GRs), is defined as migration of gingival margin to apical aspect with exposure of root surface [3], is a problem that affects the majority of adults in populations. GRs have been classified by several authors [4] and the most preferred classification of the GRs in the last decades probably classification by Miller [5]. Lately, GRs has been reevaluated at "Periodontal Manifestations Of Systemic Diseases And Developmental And Acquired Conditions: Consensus report of Workgroup 3 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions" in the section of "Mucogingival Conditions Around Natural Dentition"[3]. Workgroup 3 of the 2017 World Workshop proposed novel classification of Cairo at all. [6] with with reference to the interproximal clinical attachment level loss on the Classification of Periodontal and Peri-Implant Diseases and Conditions [3].

GRs can be determined as single and multiple by the number of affected teeth. GRs have several etiologies that can be grouped in: anatomical factors (e.g., lack of attached gingival, muscular insertions, tooth

misalignment, inadequate thickness of the alveolar bone plate and root prominences; (e.g., periodontitis or viral infections); iatrogenic factors (e.g., improper restorations) and mechanical trauma (e.g., toothbrushing trauma or lip piercing) [4]. In the new classification, periodontal health was defined free from tissue inflammatory status, based on World Health Organisation [7]. Thin phenotype ( $\leq 1\text{mm}$ ) has been demonstrated being a risk factor for GRs [3]. Some studies reported a positive association, some a negative, and some no association between GRs and tissue thickness [3]. Jepsen et al [3] reported that different orthodontic movement might be significant risk factor for the the soft tissue injuries of thin bucco-lingual gingival thickness.

### Management of GRs

Until today, clinicians and researchers revealed an increasing curiosity in mucogingival and periodontal plastic surgery to restore soft tissue around teeth and implants. Mucogingival therapy is a general term that depicts periodontal treatment involving procedures for correction of mucosal defects, amount of soft tissue and underlying bone support around teeth and implants [8]. Mucogingival surgery introduced by Friedman in 1957 [8], included surgical approaches to save gingival tissue, eliminate frenal or muscle attachments and boost the depth of the vestibule. Periodontal plastic surgery term initially suggested by Miller in 1993, was defined as “surgical procedures performed to prohibit or correct anatomic, developmental, traumatic or disease-induced defects of the gingiva, alveolar mucosa or bone” [9]. This definition involves manifold soft- and hard-tissue procedures; soft tissue augmentation, root coverage, elimination of mucosal recessions around dental implant, crown lengthening, gingival preservation of ectopic tooth eruption, removal of frenal attachments, socket preservation after tooth extraction and bone augmentation of the edentulous ridge.

GR can be treated with various surgical techniques and root coverage can be obtained. Height of the interdental periodontal tissue, including (interproximal bone level and clinical attachment) is the key factor for evaluation of root coverage [5].

Periodontal health along with sufficient keratinized gingival and gingival thickness, complete root coverage and aesthetic integrity is considered to be the essential aims in the treatment of GR [10]; whereas aesthetic demands, dentine hypersensitivity and obtaining sufficient keratinized tissue support have been the most indications for the treatment of GRs.

Takei et al. [11] classified root coverage procedures in the treatment of GR as follows:

#### Pedicle Grafts (Pedicle Flaps)

##### Rotation Flap Procedures

- Laterally Sliding Flap<sup>[12]</sup>,
- Double Papilla Flap Technique<sup>[13]</sup>,
- Oblique Rotated Flap<sup>[14]</sup>.

##### Advanced Flap Procedures

- Coronally Advanced Flap (CAF)<sup>[15]</sup>,
- Semilunar Advanced Flap<sup>[16]</sup>.

### Free Grafts

#### Free Gingival Graft (FGG) (Bjorn 1963)

- Single stage (FGG)<sup>[17]</sup>,
- Double stage (FGG + CAF)<sup>[15]</sup>.

#### Subepithelial Connective Tissue Graft<sup>[18]</sup>,

- Subepithelial Connective Tissue Graft + Rotation Flap<sup>[19]</sup>,
- Subepithelial Connective Tissue Graft + Pouch Technique<sup>[20]</sup>,
- Tunnel Technique<sup>[21]</sup>.

#### Root Surface Bio-modification Therapy

- Citric Acid<sup>[22]</sup>,
- Tetracycline Hydrochloride<sup>[23]</sup>,
- EDTA Fibrin-Fibronectin Complexes<sup>[24]</sup>.

#### Biomimetic Approach

- Enamel Matrix Protein Derivatives (EMD)<sup>[25]</sup>,
- Acellular Dermal Matrix Allograft (ADM)<sup>[26]</sup>,
- Guided Tissue Regeneration (GTR)<sup>[27]</sup>.

**Laterally Sliding Flap.** This technique has been initially proposed by Grupe & Warren [12], is advocated when the local anatomic condition disallowed the CAF technique. The laterally sliding flap is commonly used to cover isolated, denuded root surface that has sufficient lateral donor tissue volume and vestibular depth. Various modifications [28] have been proposed to avoid the reported undesirable results on the donor teeth.

**Double Papilla Flap Technique.** Cohen et al. [13] suggested in 1968, Double Papilla Flap technique for the treatment of localized gingival recessions. This technique mostly preferred for treatment of isolated recessions offers the advantages of dual blood supply and prevent permanent damage interproximal are after surgical exposure. It also offers the advantage of patient morbidity and reduces the risk of facial bone height loss.

**Oblique Rotated Flap Technique.** This procedure facilitates to manage gingival recession without gingival grafts. Oblique rotation flap operation, which is a modification of the horizontally repositioned flap and other advanced procedures. This technique provides to obtain sufficient keratinized tissue, in addition, eliminates aberrant frenal attachment [14].

**Coronally Advanced Flap (CAF).** The CAF procedure is very popular and most acceptable approach for root coverage. Coronal shift of marginal tissue complex on the denuded root surface has revealed the name of the technique. CAF technique initially was defined by Norberg in 1926. This technique was first described and published by Bernimoulin [15] in 1975. As a result, the exposed root surface is tried to be covered by repositioning the mucosal flap via the coronal direction. Conditions required to perform the CAF procedure are the presence sufficient height (1 mm for shallow recessions, 2 mm for severe recession  $\geq 5$  mm) [9] and thickness of keratinized gingival at apical area [29]. Zucchelli & De Sanctis modified this technique and described novel approach – Modified CAF technique [30].

**Semilunar Advanced Flap.** Semilunar technique was defined by Tarnow[16]. In this method, semilunar incision has been performed to parallel the root surface minimum 2-3 mm away from the gingival papillae. Followed by, the partial thickness flap shifted coronally to cover the exposed root surface.

**Free Gingival Graft.** The free gingival grafting (FGG), first described by Bjorn in 1963, is the most effective procedure to increase the width of attached gingival recession area [31]. FGG is mostly used when the main goal of the surgical procedure is to augment attached gingiva height, but undesirable aesthetic results and incomplete root coverage should be taken into account.

**Root Biomodification.** The main goal of using the root surface biomodifiers is exposing the collagen fibers by the cement to increase the fibrin connection between the graft or flap and the root surface. Mariotti reviewed evaluation effects of biomodifications on the root surface [32]. Consequently, effectiveness of citric acid, tetracycline-HCl, fibronectin and EDTA on the root surface is not evidence for a conclusive evaluation [32].

**Biomimetic Approach.** Studies indicated that enamel related proteins induced formation of cementum in periodontal regeneration process. Enamel Matrix Derivatives Proteins (EMD) are expressed from Hertwig epithelial cells and induce cementogenesis [25]. Emdogain (Straumann, Basel, Switzerland), is the only FDA approved product, is a purified acidic, containing amelogenins that can be applied to the root surface through the propylene glycol alginate release system.

**Acellular Dermal Matrix Allografts.** Acellular dermal matrix allograft (ADM) is derived from dermis layer of human skin tissues consisting of cell-free, frozen-dried, collagen and elastin fibrils. ADM is widely accepted for root coverage in the treatment of gingival recessions. Using FDA proved ADM allograft AlloDerm provides to increase gingival thickness and root coverage [26].

**Guided Tissue Regeneration (GTR).** Production of barrier membranes brings about to commence GTR procedure on the treatment of gingival recessions. In the treatment of gingival recessions, both of resorbable and non-resorbable barrier membranes are used. Membranes provide to create a gap space causes tissue regeneration on recession region. For the first time, barrier membranes are used for root coverage by Pini Prato et al. [27] in 1992.

## Tunnel Technique

The treatment of multiple GRs, encountered many challenges, such as different anatomical contours, the large surgical area, the diversity of keratinized gingival volume the requirement of large grafts and inadequate thickness of fibro-palatal mucosa. These difficulties cause attempts to improve variety of treatment methods in periodontal plastic surgery. Also, treatment of multiple recessions must consider the total number of surgical procedures, the amount of donor tissue that can be obtained from the palate and patients' esthetic requests.

Raetzke reported the first "Envelope technique" for root covering isolated gingival recession in 1985[20]. Raetzke performed the treatment of single gingival recessions and evaluated 12 gingival recessions area in a total of 10 patients in the case series. Split-thickness flap elevated and an envelope bed was prepared, CTG, then CTG was fixed with cyanoacrylate without suturing and periodontal dress [20]. After 8 months, average root coverage was 80%. As a result, it has been suggested that the "envelope" technique is the preferable method in the treatment of single gingival recessions.

Later on, Allen [14] created a partial-thickness suprapariosteal envelope and modified the envelope technique in the treatment of multiple gingival recessions his case report in 1994 [21]. In this method, sulcular incisions were used to the papillary complex as an internal bevel. Partial-thickness suprapariosteal envelope was extended 3-5 mm lateral and apical directions away from recession area. After harvesting palatal graft, CTG was inserted in the suprapariosteal envelope and the papillary complex and graft were fixed with vertical matrix sutures. In this method, it has been reported that the papilla elevation causes the movement of flap coronally.

Azzi et al.[33] modified the Allen method and reported coronally advanced modified tunnel technique. In this study, CTG harvested from tuberosity area. Interdental areas in the relevant area with gingival recession temporarily splinted with composite. The graft and gingiva-papillary complex were coronally advanced, fixed with 4.0 silk sutures using a vertical matrix technique. Later on, horizontal matrix sutures were performed [33].

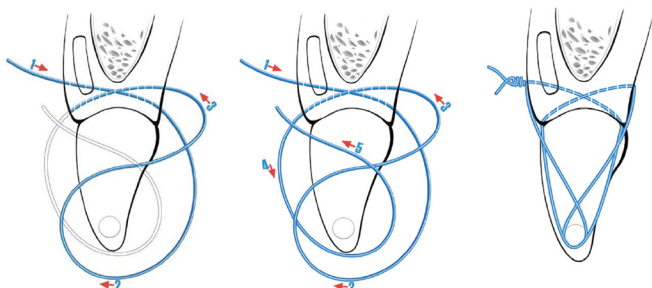
Although Allen's [21] paper is considered the first "tunnel method" in the history of tunnel technique, Zabalegui et al. later coined the first term "tunnel" in periodontal plastic surgery [34]. Zabalegui et al. described papillary partial-thickness elevation made multiple envelope tunnels in the treatment of Miller class I and II gingival recessions [34]. Partial-thickness papillary elevation was performed with sharp dissection extended 3-5 mm to mesial, distal and laterally. CTG inserted tunnel recipient bed with auxiliary sutures and fixed vertical mattress sutures on the both of terminal.

As a result, this method reported representing highly predictable results in the treatment of multiple and single gingival recessions[34].

Zuhr et al. [35] represent to develop a microsurgical approach and new tunnel instrumentation in periodontal plastic surgery. In this case report, authors described creating a tunnel bed through suprapariosteal elevation of buccal gingivopapillary complex following sulcular incision. Microsurgery sharp tunnel instruments provide dissection of the entire buccal aspect is performed as a mucosal flap without perforation. CTG harvested from hard palate through "single incision technique" [36]. After immediately CTG inserted in tunnel bed with supportive sutures and microsurgical instruments. The gingivo-papillary complex was shifted to the coronal position and fixed with vertical matrix sutures. As a result, modification of method and microsurgery instruments increased aesthetic outcomes on the tunnel procedures [35].



Zuhr et al. [37] reported novel modification suture technique-double crossed sutures in tunnel technique. This suture technique provides the opportunity to stabilize the gingivo-papillary complex in a coronal position and to improve adaptation flap-graft unity to root surface [37].



**Figure 1.** Double-crossed suture technique: penetrate from buccal side (1) to the palatal side and wrapping around the contact point (2), back to the palatal side (3). Again starting from the palatal side to the buccal side (4), wrapping around the contact point and passing underneath the contact point back to buccal side (5).

Aroca et al. [38, 39] proposed the “coronally advanced modified tunnel technique” includes a mucoperiosteal flap elevation that separates papillae from interproximal bone tissue. Aroca et al. reported the treatment Miller class III multiple gingival recessions total of 139 regions of 20 patients in their randomized clinical trials. Twenty healthy subjects with a mean age of 31.7 years, were enrolled for the trial in a university periodontal clinic. Patients with at least three adjacent gingival recessions on both sides of the mouth were treated with a modified tunnel/CTG technique. On the test side, an EMD was used in addition. Clinical parameters were measured at baseline, 28 days, 3, 6 and 12 months after the surgery. Gingival recessions in the test group were treated by CTG + Modified tunnel technique + EMD, only CTG + Tunnel technique results were evaluated in the control group. Average root coverage 83% in the test group and 82% in the control group. Aroca et al. [39] reported that, Tunnel technique was predictable technique in Miller class III treatment.

Aroca et al.[38] reported to involve twenty-two patients with a total of 156 Miller Class I and II gingival recessions in this study. Recessions were randomly treated according to a split-mouth design by means of MCAT(modified coronally advanced tunnel) + CM (collagen matrix) (test) or MCAT + CTG (control). The following measurements were recorded at baseline (i.e. prior to surgery) and at 12 months: Gingival Recession Depth (GRD), Probing Pocket Depth (PD), Clinical Attachment Level (CAL), Keratinized Tissue Width (KTW), Gingival Recession Width (GRW) and Gingival Thickness (GT). GT was measured 3-mm apical to the gingival margin. Patient acceptance was recorded using a Visual Analogue Scale (VAS). The primary outcome variable was Complete Root Coverage (CRC), secondary outcomes were Mean Root Coverage (MRC), change in KTW, GT, patient acceptance and duration of surgery. No statistically significant difference in the rate of CR for both

groups (control group 85% of the test group 42%) has been reported. As a result, the present findings indicate that the use of CM may be an alternative to CTG. Using CM to reduce surgical chair time and patient morbidity but the success rate is low in a long time has been reported [38].

Sculean and Allen [40] developed a new technique-Lateral Closed Tunnel (LCT) in the treatment of mandibular localized gingival recession. In this method, a mucoperiosteal pouch were prepared via microsurgical scalpel with a sulcular incision on the gingival recession canine tooth. The tunnel (pouch) bed was extended beyond the mucogingival line and mesiodistally. Emdogain (Emdogain, Straumann, Basel, Switzerland) was applied after the root surface. CTG was harvested according to the size of the recession site and sutured to the tunnel area using a modified matrix suture method. This study included 24 patients, Miller class I, II, and III gingival recession. After 12 months, CRC rate was 70.83% on 17 gingival recession sites. As a result, the LCT method is a predictable new tunnel modification in the treatment of deep mandibular Miller class I, II and III gingival recessions [40].

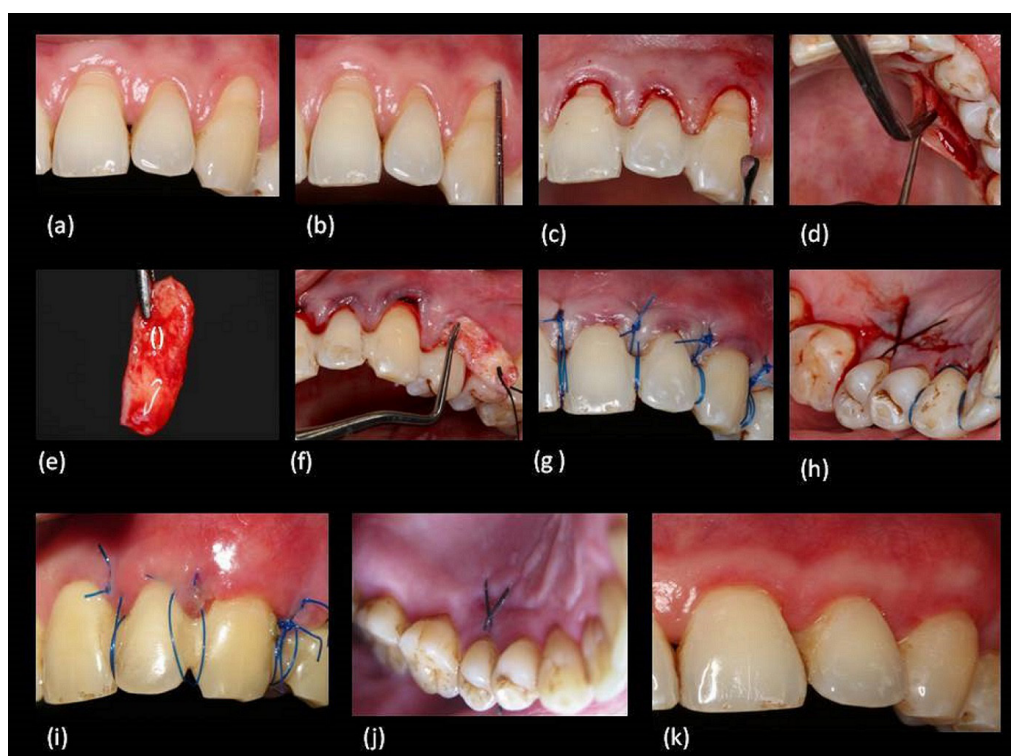
Azaripour et al. [41] showed a comparison of the CAF + CTG and modified tunnel + CTG methods in the treatment of Miller class I and II gingival recession. A total of 71 gingiva recession sites were treated in 40 patients. End of 12 months, has been reported that there was no significant difference on the CRC (CAF 97% and Tunnel 98%) at both groups.

Tavelli et al. [42] reviewed the predictability and effectiveness of the tunnel technique in the treatment of multiple and single gingival recessions in their meta-analysis study. As a result, the tunnel technique was high effectiveness pathway on the treatment of single and multiple gingival recessions, has been reported in meta-analysis research [42]. Many modifications of the tunnel technique, such as half-thickness flap elevation, microsurgery approach provide to increase final results and predictability [42].

Pathway of the tunnel surgical procedure:

- The tunnel bed is prepared with a sulcular incision at each area of recession region involved in the procedure. Tissue elevation beyond the mucogingival junction in order to obtain a tension-free tunnel, allowing the insertion of the graft.
- CTG is harvested from the palate, to obtain a graft long enough to achieve root coverage of all involved teeth. Incision can be extended from the canine area to the tuberosity
- CTG inserted into the tunnel bed by applying a auxiliary sutures with both sides.
- CTG is slightly moved into the tunnel bed, sliding under the interdental papillae. Tunnel instruments may help to adapt the graft into the tunnel.
- Graft and gingivopapillary complex was stabilized with “double vertical cross” sutures.

Figure 2 shows a complex clinical case of multiple gingival recessions treated using the connective tissue graft + tunnel technique.



**Figure 2.** Surgical approaches to multiple gingival recessions with tunnel technique. (a) Baseline image of Miller class I defects on upper right anterior teeth. (b) Measurement of gingival recession depth. (c) Gingivo-papillary elevation via tunnel microsurgery knives. (d) Single incision procedure to CTG harvesting. (e) Harvested CTG. (f) Graft insertion into tunnel bed. (g) Double vertical cross suturing image. (h) Post-surgical primary closure of donor area. (i) One-week post-surgical image recession region. (j) One-week post-surgical image donor area. (k) A 12-month post surgical image.

### Graft Selection

In the presence of multiple defects, the attempt to reduce the number of intraoral surgical sites, together with the need to satisfy the patient's esthetic demands, must always be taken into consideration. Thus, when multiple recessions affect adjacent teeth they should be treated at the same time and, if possible, the removal of soft tissue from distant areas of the mouth (palate) should be minimized to reduce patient discomfort [4]. Therefore, successful outcomes have been reported simultaneous harvesting and using CTG and de-epithelization FGG on the treatment of gingival recession with tunnel technique [43, 44]. The subepithelial connective tissue graft is a predictable and versatile technique in treatment of gingival recessions. Initially, Edel [45] suggested that, subepithelial connective tissue carries the necessary genetic message for keratinization. Langer and Langer [18] describe using CTG for root covering in 1985. Some surgical techniques have been applied and improved to harvest CTG; "trap to door" [45], "L technique" [46] and "single incision technique" [36].

The advantages CTG harvesting comprises primary closure healing of the donor area, the patient's low post-operative pain and discomfort, sufficient blood supply in the recipient site and aesthetic tissue chromatinization. Chambrone et al. [47] revealed that, subepithelial connective tissue grafts provide significant root coverage, clinical attachment and keratinized tissue gain in systematic review. Overall comparisons allow us to consider it as the 'gold standard' procedure for root coverage in periodontal plastic surgery [47-49].

The most important disadvantages of this technique are the need for an additional donor area and the surgical technique requires enough surgical experience. In addition, the healing

period has been concluded usually with a long junction epithelium, and a small amount of connective tissue attachment [19]. Pasquinelli [50] reported to increase new attachment, the amount of cement and alveolar bone after treatment of gingival recessions with CTG.

Besides, the traditional methods of using CTG with tunnel technique in the treatment of gingival recessions, many alternative products as de-epithelialized palatal grafts, collagen matrix, acellular dermal allo- and xenografts have been studied [38, 44, 51, 52]. When palatal fibromucosal tissue thickness was insufficient ( $\leq 2.5$  mm), apico-coronal or mesiodistal sizes grafts were required [32, 39-42, 44, 47, 156], de-epFGG may be an alternative to CTG. Bertl et al. [53] showed that, de-epithelialized palatal grafts contain higher amounts of dense collagen and connective tissue and low amounts of glandular and adipose tissue compared to conventional CTG, as a result of histomorphometric analysis. Therefore, minimum tissue shrinkage and graft resorption have been reported [54]. Azar et al. [55] reported that, de-epFGG could be considered as "predominantly dense CTG", included minimum adipose and epithelial tissue. Evaluation of epithelial tissue remnants on long term clinical outcomes requires further clinical research [55, 56]. Tavelli et al. [57] showed to obtain high mean RC, KT and clinical attachment level (CAL) results with de-epithelialized palatal graft +CAF than CTG. McLeod et al. [44] initially used de-epithelialized palatal graft with tunnel technique on the treatment of mandibular Miller class I and II gingival recessions. McLeod et al. [44] reported that, this procedure is practical than other CTG harvesting technique, using a de-epFGG result in to increase KT, gingival thickness and average RC 80-100%.

## Conclusion

To the important author's research, this review presents unique places of tunnel technique in periodontal-plastic surgery. Tunnel technique is highly effective in treating gingival recession defects. Tunnel technique provides treatment of gingival recessions without vertical incision and scar tissue formation, especially anterior zone. Tunnel technique ensures better blood supply, which improves wound healing, graft fusion, causes successful root coverage and CAL gain. Periodontics should carefully examine every method before cases. Surgical experience, microsurgical approach and technique modification may improve final outcomes.

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# Missed opportunities in the assessment and management of suicidal youth in a developing country

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**Background:** High rates of suicide reported for youth in South Africa. As suicide attempters share similarities with suicide completers, it is important to establish their characteristics as this has implications for the provision of services and intervention programmes in a developing country.

**Aim:** The aim was to identify youth at high risk for future attempts and to provide guidelines for the management of at risk youth

**Material & methods:** A 5 year retrospective chart review was undertaken to establish the socio-demographic profile and associated factors of suicide attempters aged 18 and under seen at the Psychology and Psychiatry departments of a tertiary public hospital in the Durban, South Africa. The Diagnostic and Statistical Manual of Mental Disorders (DSM) system was utilized.

**Results:** Of the 555 patients under the age of 18 who were seen over a five year period, 13.3% (n =74) were seen following a suicide attempt. The majority reported previous suicide attempts, but less than one third of these had seen a mental health care professional (MHCP) for these previous attempt/s. Relationship problems with parents or partners constituted the majority of the diagnoses but severe mental illnesses, mood disorders in particular, were also present.

**Conclusion:** All youth presenting to health facilities with a suicide attempt should be admitted and referred to MHCP for further assessment and management in order to prevent further attempts. Health care providers, such as emergency personnel should also be capacitated to screen and identify high-risk youth. Issues addressing the gaps between needs and services are discussed.

**Keywords:** suicide attempts, children, LAMIC, mental illness, relationship issues

## Background

Suicidal behaviour which encompasses suicidal ideation, plans, attempts and completed suicide is a significant public health problem globally and in South Africa [1]. Approximately 86% of the 800 000 of global suicides occur annually in low and middle-income countries (LAMIC) [2] such as South Africa. The national suicide statistics in South Africa indicate that the rate for children and adolescents between the ages of 5 to 14 years is 1.4 per 100, 000, but increases significantly to 17.6 per 100 000 for those aged between 15 to 29 years [3]. The estimated ratio of a suicide to a suicide attempt is 1: 20 for all age groups [4].

Suicide statistics for the city of Durban indicate that 2.4% of those who committed suicide between 2006 and 2007 were under 14 years of age [5]. While these statistics may be low, they may not indicate the true extent of the problem due to poor surveillance and reporting systems [2] and the use of outdated data [3,5]. Factors such as fear of stigmatizing the survivors of suicide and cultural and religious taboos on suicide also prevent accurate reporting [6].

These high suicide rates have led to the establishment of a national suicide prevention programme as one of the key areas identified by the South African Department of Health National Mental Health Policy

Framework Strategic Plan, 2013 to 2020 ([www.health-eorg.za](http://www.health-eorg.za)). Successful implementation of this program requires the identification of “at risk” individuals, which presents some challenges. While much research has been conducted on suicidal behavior, including suicide in high-income countries, research in developing countries such as South Africa is limited [7,8]. This is partly due to the marginalization of non-communicable diseases such as mental illness when faced with pandemics of infectious diseases such as HIV/AIDS and tuberculosis [10]. The research conducted on suicidal behavior in South Africa has shifted away from clinical or hospital based studies to assessing suicidal behavior in community samples [7,8,9]. However, hospital based research on suicidal behavior is necessary as it provides information to inform and improve clinical care/services, plan targeted public health prevention and intervention strategies as well as healthcare policies, including teaching and training of various healthcare and other professionals in this area.

Clinical studies indicate that up to one-third of non-fatal suicidal attempts involve children and adolescents [11]. Further, as suicide attempters share remarkable similarity with suicide completers [12] and that persons who have made a suicide attempt frequently re-attempt and are at significant risk of subsequently demising from suicide [12,13], it is crucial that those challenged by the problem of youth suicide need to understand the characteristics of young suicide attempters in their local contexts.

In both community and clinical studies conducted in various parts of South Africa, factors such as family conflict [14], interpersonal conflict [15], school-related problems such as failure and bullying [1] and rigid problem-solving behavior, over-controlling parental styles and lack of tolerance by parents or caregivers for developmental/ role changes [14] have all been identified as correlates of suicidal behavior. Other correlates such as parental loss through divorce or parental death, a family history of psychopathology (including substance use) [1], poor perceived parental support and negative feelings about the family [7], and past peer and family suicide attempts [16] all play a role.

However, some research has been conducted with small, qualitative community samples in other parts of South Africa [16], while much of the hospital research has been conducted in the late 1990's and mid 2000's more current research is needed [11, 14].

## Aim

The aim was to undertake a five-year retrospective chart review of all under 18-year-olds admitted to a public, tertiary hospital following a suicide attempt. This is in order to develop a better understanding of suicide attempters' socio-demographic and associated factors in a clinical sample to assist in intervention and prevention measures.

## Material & Methods

A retrospective chart review of all patients under the age of 18, a total of 555, who had attended the Psychology and Psychiatry departments of a public tertiary hospital over a randomly

chosen five-year period were screened to identify those admitted following a suicide attempt. A total of 74 charts (13.3%) of patients admitted to a tertiary hospital following a suicide attempt were reviewed and their data extracted. Ethical approval was obtained from the Biomedical Research Ethics Committee (BREC), University of KwaZulu Natal (BE Number: 325/13).

All 74 patients were first admissions to this particular hospital for a suicide attempt and were admitted to the relevant wards (generally medical and surgical wards). They were assessed by clinical psychologists and /or psychiatrists (mental health care practitioner-MHCP) as inpatients, once medically stable and prior to discharge. The investigators recorded clinical interviews detailing socio-demographic factors, the attempt, diagnoses and management plans. The Diagnostic and Statistical Manual of Mental Disorders (DSM IV TR) was used for diagnoses. Data has been analyzed using SPSS Statistics®.

## Results

Of a total of 555 patients under the age of 18-year who were assessed by the Psychiatry and Psychology Department of a major tertiary hospital over a 5-year-period, 13.3% (n=74) were assessed after being admitted for a suicide attempt. This paper presents the data of these 74 suicide attempters below.

The mean age of the suicide attempters (n =74) was 14.64 (SD 2.25; range: 9 - 17.11 years). Females constituted the majority of the sample at 77% (n=57). In terms of ethnicity, the sample was a diverse one. The majority were Blacks (68.9%; n= 51), followed by Caucasians (13.5%; n= 10), Indians (descendants of settlers from the Indian subcontinent ) ( 12.2%; n =9 ) and then “Coloured” South Africans (descendants of mixed Black and Caucasian ethnic origin) [17] (5.4%; n=4 ). The majority of the sample (87.8%; n=65) self- identified as following the Christian faith, followed by those practicing Islam (6.8%; n=5), with Hinduism and African traditional religion at 2.7% (n =2) each.

Just over 35% (n =26) had previous contact with a MHCP. Of these, almost 26% (n=19) had a past psychiatric diagnosis. Of the total sample (n=74), 37.8% (n=28) reported previous suicide attempts, ranging from 1 to 6, with the majority 64.3% (n=18) reporting more than 2 previous suicide attempts. Of those reporting prior attempts, only 32% (n=9) had been seen by a MHCP following the attempt/s. A family history of mental illness was reported by 28.4% (n =21) of the suicide attempters, most involving parents (17.6%; n=13). A family history of suicide was reported by 4.1% (n =3), while 8.1% (n=6) reported that family members had made suicide attempts.

Ingestion of substances (n=55; 74.3%) such as over -the-counter medication, paraffin and pesticides was most common method used for the attempt, followed by hanging (n=8;11%), cutting (n=6; 8%) and jumping from heights (n=2; 3%). Four percent used combinations of the above methods.

The most common precipitants for the attempt were conflict with family at 44.6% and self-reported depression and perceived lack of support from family at 10.8% each, respectively. Sexual abuse and physical or emotional abuse was reported by (16.2%, n =12) of the sample. School problems such as poor academic performance and bullying were reported at 9.50% while conflict



with others (at school and with friends etc.) was at 4.10% and grief-related issues were at 2.70%. Almost 15% reported the use of substances such as alcohol, cigarettes, including 6.8% who reported the use of other illegal substances (marijuana, ecstasy).

In terms of provisional psychiatric diagnoses using DSMIV-TR, comorbid diagnoses were evident. V Code diagnoses such as Relationship issues between parent and child or partner relationship problems predominated at 43.2% (n=32). The second largest category were mood disorders: Major Depressive Disorder (MDD) and Dysthymia which were reported in 29.8% (n=22) and Bipolar Mood disorder in 8.1% (n=6) of the sample.

Borderline personality traits (28.4%, n =21) and Adjustment disorder was diagnosed in 10.8 % (n=8) of the sample. Attention Deficit Disorder was diagnosed in 6.8 % (n=5 ). Post -Traumatic Stress Disorder (n=3) and Acute Stress Disorder (n =1) was diagnosed in a total of 5.5 % of the sample. Conduct disorder in 8.1% (n=6) of the sample and Oppositional Defiant Disorder constituted 5.4 % (n=4) of the diagnoses. Schizophrenia and schizoaffective disorder constituted the remainder at 1.4% (n=1) each respectively. Substance induced and substance intoxication each constituted 1.4 % of the diagnoses. Intellectual disability was diagnosed in 2.7 % (n=2) of the sample.

In terms of management, 17.57% (n=13) were admitted to either a child or an adult psychiatric unit (if over the age of 12 years) for further holistic management. Outpatient treatment was provided to the others (n=16; 82.43 %). Almost 93% (n=68) of suicidal youth received psychotherapy as inpatients and continued this as outpatients upon discharge. Of the sample, 34 % (n= 25) were prescribed psychotropic medication, while 38% (n =28) were referred to social workers. The findings are presented in Table 1.

## Discussion

The findings indicate that just over 13% of youth between the ages of 9 and 18 years seen by mental health care professionals (MHCP) over a five year period in a government tertiary hospital were admissions following a suicide attempt.

A significant percentage of suicide attempters had previous contact with MHCP and also had a psychiatric diagnosis. Research indicates that almost any diagnosable psychiatric disorder increases the risk for suicide [18]. Of concern is that less than a third of current youth suicide attempters who had a prior history of suicide attempts had seen a MHCP for these previous attempts. It appears that suicide attempters were either not taken to hospital following previous suicide attempts or were attended to medically but not referred to any MHCP for the prior attempt/s. This indicates missed opportunities for routine screening and clinical detection of youth for suicidal behaviors or related mental disorders in general medical settings. Given that persons who make a suicide attempt, frequently re-attempt and are at great risk of subsequently demising from suicide [12, 13]. This indicates missed opportunities for routine screening and clinical detection of youth for suicidal behaviors or related mental disorders in general medical settings when the initial suicide attempt occurred.

**Table 1.** Characteristics of research subjects.

| Characteristics  | n  | Percentage (%) |
|--|----|----------------|
| Gender:  |    |                |
| Male   | 17 | 23             |
| Female   | 57 | 77             |
| Ethnicity:   |    |                |
| Blacks   | 51 | 68.9           |
| Whites   | 10 | 13.5           |
| Indians  | 9  | 12.2           |
| Coloured   | 4  | 5.4            |
| Previous contact with MHCP                             | 26 | 35             |
| Past psychiatric diagnoses                             | 19 | 25.7           |
| Family history of:                                     |    |                |
| mental illness   | 21 | 28.4           |
| suicide  | 3  | 4.1            |
| suicide attempts                                       | 6  | 8.1            |
| Previous suicide attempts                              | 28 | 37.8           |
| Contact with MHCP following previous suicide attempt/s | 9  | 32             |
| Method used in suicide attempt:                        |    |                |
| Ingestion of substances/tablets                        | 55 | 74.3           |
| Hanging  | 8  | 11             |
| Cutting  | 6  | 8              |
| Jumping from heights                                   | 2  | 3              |
| Combinations of the above methods                      | 3  | 4              |
| Provisional Diagnoses (comorbid):                      |    |                |
| V Code diagnoses                                       | 32 | 43.2           |
| Major Depressive Disorder (MDD) and Dysthymia          | 22 | 29.7           |
| Adjustment disorder                                    | 8  | 10.8           |
| Borderline personality traits                          | 21 | 28.4           |
| Bipolar Mood disorder                                  | 6  | 8.1            |
| Attention Deficit Disorder                             | 5  | 6.8            |
| Post -traumatic Stress and Acute Stress Disorder       | 4  | 5.5            |
| Oppositional Defiant Disorder                          | 4  | 5.4            |
| Conduct disorder                                       | 6  | 8.1            |
| Schizophrenia and schizoaffective disorder             | 2  | 2.7            |
| Substance induced and substance                        | 2  | 2.7            |
| Cognitive impairment/Intellectual disability           | 2  | 2.7            |
| Conversion disorder                                    | 1  | 1.4            |
| Management:  |    |                |
| Admissions to a child or an adult psychiatric unit     | 13 | 17.6           |
| Outpatient treatment (psychiatry and psychology)       | 61 | 82.4           |
| Psychotherapy (individual and/or family)               | 68 | 93             |
| Psycho-tropic medication                               | 25 | 34             |
| Referral to social workers                             | 28 | 38             |

One possible reason for the low numbers referred to MHCP on first attempt could be the severe shortages of health professionals and MHCP in South Africa [2]. Over-burdened health professionals such as emergency medical physicians may not refer as they may not have the skills to assess or screen. South Africa has per 100 000 population: 0.28 psychiatrists, 0.32 psychologists, 0.40 social workers, 0.13 occupational therapists and 10 nurses, most of who are working in urban areas [2]. As far back as 2006 when the population was much lower, research indicated that South Africa was short of 646 psychiatrists and 466 psychologists [19].

Furthermore, resources for children and adolescents are even more limited with only 1.4% of outpatient facilities, 3.8% of acute beds in general hospitals and 1% of beds in psychiatric hospitals being designated for children and adolescents [2]. In the Durban metropolitan area where this study was conducted, only 2 child psychiatrists work in government hospitals [2].

Lack of funding for mental health services prevents the development of key services such as child and adolescent mental health services. This condition currently results in only 4 in-patient child and adolescent psychiatry beds being available in Durban [20]. It creates an “elitist” service, which fragments the limited mental health services available even further. Community based mental health services and psychosocial rehabilitation services are also lacking [2]. This also places the burden of care back again on MHCP in general hospitals already severely under-resourced or on limited non-governmental organizations. Thus, there is a clear gap between mental health needs and services[2], and not much progress has been made since the abovementioned data [20] was published to date.

Another possible reason for suicide attempters not seeing any MHCP following the attempt, could be that mental health issues in South Africa are generally under-diagnosed and untreated. More than half of South Africans do not consider mental health as a priority [19]. Furthermore, although South Africa is classified as an upper-middle-income country, it has the highest inequality level in the world. It has a GINI coefficient of 0.70, that is, the poorest fifth of the population account for 2% of the country's income and consumption, and the wealthiest fifth for 72% [21]. In the face of poverty, unemployment, violence, trauma and communicable/ non- communicable diseases, mental health is either low or not on the list of priorities. To contextualize this, of the nine provinces in South Africa, KwaZulu Natal has the highest risk for mental illness: it has the highest proportion of people living below the poverty line, highest poverty gap, third-highest unemployment rate, has the highest prevalence of HIV/AIDS in South Africa and the second highest murder rate. Of the six major cities in South Africa, Durban also has the second highest suicide rate for males [20]. Yet, hospital budgets do not reflect this reality in terms of mental health services. Furthermore, social stigma and religious and cultural taboos associated with the use of mental health services may also play a role in access to services[1,2].

Severe mental illness, such as mood disorders, major depressive disorder, dysthymia, and bipolar mood disorder, also emerged as a significant diagnosis in this study. Family histories

of mental illness, suicide attempts and suicide were reported in this study. The suicidal behaviour of adolescents is correlated with their relatives' suicide rate [22] with familial clustering of suicidal behaviour having a partly genetic basis with heritability estimates of 17–55% for suicidal behaviour and 20% for suicide [23]. Suicide attempts are also more likely to be associated with a family history of impulsive, aggressive behaviour and mood disorder. Furthermore, research indicates that mental illness among parents and other relatives is a risk factor for suicide attempts among their offspring. A quarter of those who attempt suicide report parental psychopathology [24]. While this study did not explore the nature of parental psychopathology or parental mental illness, suicide and suicide attempts evident in this sample may render parents incapable of addressing normal childhood developmental issues experienced, (such as heterosexual relationships) and parents may be incapable of offering support when their child is experiencing other stressors. Intervention programmes need to provide support for these high risk, vulnerable parents.

Borderline personality traits, conduct and oppositional disorders were also found in this sample. Aggressive, impulsive behaviour is a major risk factor for suicidal behaviour in adolescents. There are high co-morbidity between conduct disorders, mood disorders and suicidal behaviour [18]. Developmental variations in presentation, symptomatic overlap with other disorders, a lack of clinician awareness[18] of comorbidities and/or an unwillingness to diagnose youth as mentally ill for fear of stigmatizing them, can often contribute to under or misdiagnoses in youth. Such issues also often result in missed opportunities for intervention, especially following the first suicide attempt.

The assessment of suicide attempters should also not only focus on the presence of a diagnosable psychiatric disorder or psychopathology. V Code diagnoses such as relationship issues with parents or partners constituted 43% of the diagnoses in this study. Different life events can have different effects or impacts at different ages with parent-child conflicts common stressors in early adolescence. Romantic relationships and discord therein are stressors in later adolescence. [25]. In such cases, the focus should be the prevention of further suicidal behaviour by addressing underlying precipitating factors[15]. Such stressors could render the children vulnerable to future mental illness, particularly if other cumulative stressors increase the allostatic load. Research indicates that more than 70% of child suicides between the ages of 9 and 14 years had family conflict as a trigger [12].

Youth suicide attempts may be cries for help. However, if these attempts do not have the desired effect on significant others, more attempts may be made using more lethal methods, until some resolution occurs. Some examples of these resolutions are, that the precipitants are appropriately addressed, the problems are resolved or a suicide results. In repeated cases of suicide attempts, the provision of emotional support and teaching of coping skills including the fostering of resilience and hardiness, as well as monitoring of the home situation and mentally ill parents by MHCP (including for example, community nurses) are all viable intervention strategies.

A limitation is the small sample size which may limit generalizability. However, this study adds to the research on child and adolescent mental disorders, which constitutes a small fraction of the 3% to 6% of mental health research conducted in LAMIC [26]. Further, this clinical study provides data for the development and provision of tertiary level inpatient and outpatient services for children and adolescents [20] in a LAMIC.

## Conclusion

A significant percentage of youth have made suicide attempts but have not been assessed by any MHCP's, indicating missed opportunities for early intervention and prevention of further suicide attempts. Furthermore, a significant percentage of suicide attempts were diagnosed as being severely mentally ill with family histories of mental illness, suicide attempts and suicide, which renders these youth as a "high risk" group for future suicide, but even they did not receive any mental health services initially. Individuals with such histories should be identified for routine screening and clinical detection of suicidal behaviours and mental illness by health professionals. The latter need to be capacitated in developing these skills through continued education. Given the range of provisional comorbid diagnoses and high environmental and individual risk factors for mental illness, this study indicates the need for more human resources, infrastructure and specialized, coordinated and integrated mental health inpatient and outpatient services for children and adolescents. Despite limited and fragmented mental healthcare resources and budgets in developing countries, it is recommended that youth suicide attempters should be admitted following emergency medical management and then referred to a MHCP in order to identify mental illness, intervene and prevent further suicide attempts.

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# Comparison Between Serum Procalcitonin Measurement Using Rapid Test Fluorescent Immunoassay (FIA) Method and Electrochemiluminescence Immunoassay (ECLIA) Method In Sepsis Detection

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**Objective:** Procalcitonin (PCT) is widely used as an indicator in detecting bacterial infection in sepsis, but it requires a moderately high cost and a big analyzer with a large sample capacity. It is more favorable for a laboratory in which revenue depends heavily on the national health insurance to have a small-sized analyzer, with small throughput, which can conduct a mono-test at an affordable price. We aim to compare procalcitonin values between two analyzers in sepsis cases.

**Material & methods:** A cross-sectional study was conducted in Saiful Anwar General Hospital centralized laboratory in 2018. The samples were measured for PCT with two different methods: fluorescent immunoassay (FIA) and electrochemiluminescence immunoassay (ECLIA). The results of the two methods were compared. We also examine the correlation of the results with Sequential Organ Failure Assessment or Pediatric Logistic Organ Dysfunction-2 scores.

**Results:** As many as 99 patients, consisted of 69 adults and 30 children, were diagnosed with sepsis (2 days to 85-year old). There was no significant mean difference in PCT measures between the two methods ( $p > 0.05$ ). A strong correlation was found between both methods ( $r = 0.941$ ,  $p < 0.0001$ ). There was no significant difference between the two methods for detecting sepsis in adult patients.

**Conclusion:** PCT measurement using the FIA method (FREND<sup>TM</sup> PCT) can be used for detecting sepsis in an adult patient since it has a good correlation and no significant difference with the ECLIA method (Cobas e411 Roche). Pediatric patients need special attention and further research.

**Keywords:** Procalcitonin, sepsis, FIA, ECLIA

## Introduction

Sepsis is a life-threatening critical condition in patients leading to multiple organ failure, caused by an inadequate host response to an infection [1]. Despite modern life aids and antibiotic, sepsis patient remains major problem with mortality rate around 30%–60% worldwide. It is estimated that 30 million people experienced sepsis, and in countries with lower middle income, more than 6 million neonates and children died from sepsis every year [2]. Delays in diagnosing bacterial infections and sepsis are the most decisive factors associated with poor outcomes, where confirmation of sepsis is an important element in the early management of patients with suspected

infection [3]. The latest diagnostic criteria of sepsis (Sepsis-3) are still difficult to apply because the initial identification still uses clinical signs and symptoms, such as fever, leukocytosis or leukopenia, tachycardia, and dyspnea [4,5].

Sepsis is also one of the leading causes of infant and child morbidity and mortality worldwide. The most common causes of sepsis infections in children include respiratory infections, followed by non-specific infections, bacteremia, urinary tract infections, gastrointestinal infections, central nervous system infections, as well as surgical and soft tissue. In Indonesia, the source of infection mainly comes from respiratory infections, which is 36%–42% with a higher incidence

of sepsis in the neonatal and infant groups <1 year compared with ages 1–18 years (9.7: 0.23 cases per 1,000 children). The Indonesian Pediatric Society published national guidelines for the diagnosis and management of pediatric sepsis in 2016. The diagnosis of sepsis is based on the presence of infection, including predisposing factors for infection, signs or evidence of ongoing infection, and response of inflammation; and signs of organ dysfunction or failure, which is established by pediatric logistic organ dysfunction-2 (PELOD-2) score [6]

PCT is a biomarker for an infection, has been widely used as an early stratification in patients with suspected sepsis. PCT is very helpful in antibiotic management and also has a diagnostic value on the severity of an infectious disease [7]. The prompt treatment is expected to have an impact on reducing morbidity and mortality due to sepsis and also reducing the bacterial development of antibiotic resistance [1]. Clinically, PCT greater than 2 ng/ml is associated with a high risk of sepsis and PCT less than 0.5 ng/ml is associated with a low risk of developing sepsis. All PCT measurements use standardized immunoassay techniques for Brahms PCT Luminescence Immunoassay. The automated procalcitonin test used in hospitals mostly uses different methods in detecting antibody-PCT-antibody complexes and the characteristics of each examination which are all standardized by the BRAHMS LIA measurement. Semi-quantitative PCT testing with point-of-care testing (POCT) also requires a 200 µl sample serum or plasma with the duration within 1 hour. Brahms PCT-Q uses lateral flow immunochromatography that causes reddish/brown bands that can be classified and compared with color cards [7–9]. The main obstacle for PCT measurement is that it requires a big analyzer, which is relatively expensive, with a large sample capacity. Along with technological development, currently available analyzers with small size and small throughput, mono-test, and more economical costs. It is more favorable to get results faster in simpler health facilities, especially in peripheral areas, in the era of Indonesian national health insurance [10].

There is also a FRENDS<sup>TM</sup> PCT test with quantitative PCT measurements in serum & plasma heparin, citrate, EDTA with a fluorescent immunoassay reader system. The principle of the method is a rapid test with an immunoassay sandwich with fluorescent nanoparticles. This study aims to compare the serum procalcitonin values detected with a big analyzer using the ECLIA method and the FIA rapid test (POC) method. The objective is to investigate whether the rapid test can reliably be used in detecting sepsis.

## Material & Methods

This research is cross-sectional study conducted at the Central Laboratory of Saiful Anwar General Hospital, Malang, Indonesia. Participating subjects were recruited and consented during July to December 2018. The inclusion criteria in this study were patients admitted in Saiful Anwar General Hospital, Malang, who was diagnosed with sepsis who underwent procalcitonin laboratory tests and agree to participate. Blood was drawn in a tube with separator gel, then the serum was collected and stored in –80°C refrigerator within 6 months. The exclusion

criteria were patients with highly jaundice, hemolysis, or lipemic serum. We used a consecutive sampling technique to obtain the samples.

The serum was examined for PCT levels in parallel with the FIA rapid test method using FRENDS<sup>TM</sup> PCT and the ECLIA method using Elecsys BRAHMS PCT Cobas e411 Roche. Diagnosis of sepsis is established by SOFA scores for adult patients and PELOD-2 scores for pediatric patients. The examination of PCT levels by the ECLIA method uses the sandwich principle, with a total inspection duration of 18 minutes and has a detection threshold of 0.02–100 ng/ml. The FIA method rapid test is a rapid quantitative measurement of immunoassay based on the principle of procalcitonin sandwiches on serum or plasma samples (Lithium-heparin, Citrate, and EDTA) using fluorescently conjugated nanoparticle antibodies, which form immune complexes, with procalcitonin found in patient samples. The detection threshold of the instrument is 0.07–32.00 ng/ml. The total time needed for procalcitonin examination with FRENDS<sup>TM</sup> PCT is 3 minutes. Prior to an inspection, the tool has passed quality control testing through a QC cartridge that contains several controls, including checking optical parts, laser strength, alignment, and mechanical integrity of the tool. Data were analyzed using SPSS for Windows version 25.0 and Medcalc For Windows version 14.8.1.0. p-value of <0.05 is considered as significant. A categorical comparative test of McNemar and correlation analysis of Spearman correlation test, Passing Bablok, and Bland–Altman Plot was conducted when deemed appropriate.

## Results

As many as 99 blood samples of patients newly diagnosed with sepsis were obtained. The subjects were 69 adult samples and 30 samples of children whose procalcitonin levels were examined by the ECLIA and FIA methods with the characteristics listed in Table 1. The subjects age ranges from 2 days to 85 years.

**Table 1.** Characteristics of research subjects.

| Parameter  | PCT ECLIA<br>(n = 99) | PCT FIA<br>(n = 99) |
|--|-----------------------|---------------------|
| Gender   |                       |                     |
| Male   | 51                    | 51                  |
| Female   | 48                    | 48                  |
| PCT > 2 ng/ml<br>(sample of<br>pediatric patients) | 15                    | 15                  |
| PELOD-2 score > 11                                 | 2                     | 2                   |
| PCT > 2 ng/ml<br>(sample of<br>adult patients)     | 54                    | 54                  |
| SOFA score ≥ 2                                     | 48                    | 48                  |
| PCT (Mean ± SD)                                    | 13.58 ± 13.37         | 13.82 ± 12.68       |
| PCT (CV)   | 0.98                  | 0.91                |

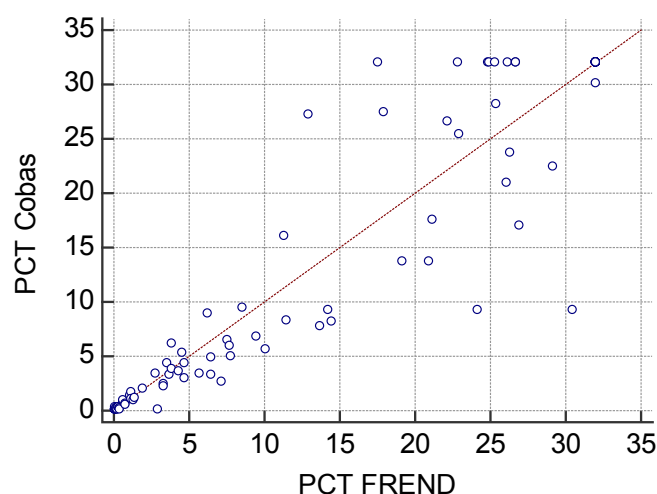
We tested all samples for data normality using the Kolmogorov-Smirnov test and obtained not normally distributed. Therefore, it continued with the Wilcoxon paired numerical comparative test, between the two methods, and the results showed no significant difference between the procalcitonin results with the ECLIA and FIA methods which can be seen in Table 2. Then, data continue analyzed with Spearman correlation test showed  $r = 0.941$  ( $p\text{-value} < 0.0001$ ) between two methods, with plot diagram, is shown in Figure 1. The agreement between the procalcitonin results with the ECLIA and FIA methods analyzed with Passing and Bablok Regression can be seen in Figure 2 and using the Bland-Altman Plot of agreement that can be seen in Figure 3.

**Table 2.** Pair t-test (Wilcoxon) test of procalcitonin by ECLIA and FIA methods.

| Parameter              | PCT FIA (n = 99)    |
|------------------------|---------------------|
| Z                      | -1.099 <sup>a</sup> |
| Asymp. Sig. (2-tailed) | 0.272 <sup>b</sup>  |

<sup>a</sup>Based on negative ranks.

<sup>b</sup>Wilcoxon Signed Ranks Test



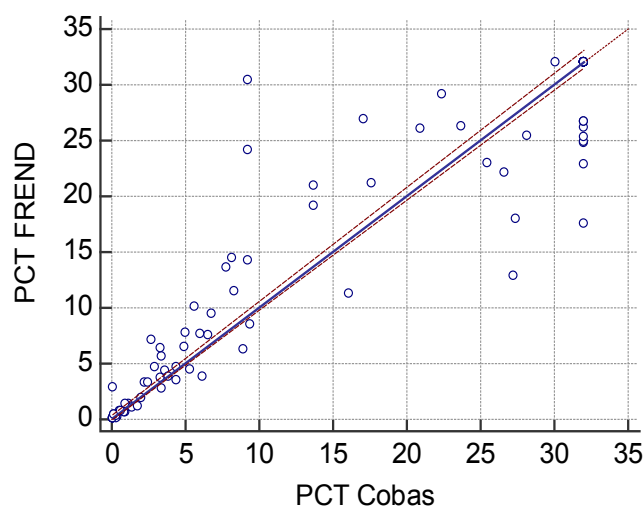
**Figure 1.** Spearman correlation test for the ECLIA and FIA methods on PCT examination.

Plot diagram of PCT measured using Cobas ECLIA method compared to FREN<sup>TM</sup> FIA method based on spearman's correlation test.

The results of the categorical comparative hypothesis test with the McNemar test on both methods are listed in Table 3.

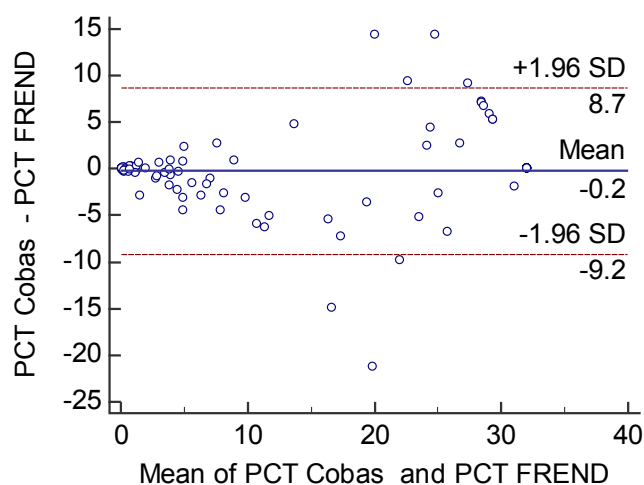
**Table 3.** McNemar test for procalcitonin examination by ECLIA and FIA methods in adult patients.

| Parameter        | Value | Exact Sig. (2-sided) |
|------------------|-------|----------------------|
| McNemar test     |       | 1.000                |
| N of valid cases | 99    |                      |



**Figure 2.** Passing and Bablok Regression ECLIA and FIA methods on PCT examination.

Passing and Bablok Regression graph of procalcitonin results in ECLIA method with Cobas and FIA method with FREN<sup>TM</sup>.



**Figure 3.** Bland-Altman plot of the ECLIA and FIA methods on PCT examination

The Bland-Altman plot agreement between the two methods for procalcitonin measurement. Axis X illustrates the mean value of procalcitonin measurements by both methods. The Y-axis illustrates the difference between the ECLIA and Cobas methods and the FIA and FREN<sup>TM</sup> methods.

## Discussion

PCT is a prehormone of calcitonin produced by thyroid parafollicular C cells that plays a role in the process of calcium homeostasis. However, PCT is also mostly produced from non-thyroid tissue as an acute phase reactant which is a response to inflammatory stimuli, especially endotoxins and lipopolysaccharides of bacteria, and several inflammatory mediators. The

role of PCT in the inflammatory response to infection is still not fully understood, but it is thought to contribute to local and systemic immune responses by modulating both immune and vascular function [7,8,10].

PCT is a calcitonin precursor polypeptide consisting of 166 amino acids with a molecular weight of 13 kDa. In healthy individuals, procalcitonin is produced by C cells of the thyroid gland and is released in the bloodstream at levels  $<0.05$  ng/l, through transcription and translation of the PCT gene, *CALC-1*, which is found on chromosome 11. The transcription process goes fast and is separated into three products, such as katacalcin, calcitonin, and terminal fragments N [7,9].

Plasma procalcitonin concentration increases with stimulation by bacterial endotoxins within 2–3 hours after bacterial invasion, because procalcitonin production is activated in all parenchymal tissues. Procalcitonin levels are stable after 6–12 hours, remain high for up to 48 hours, and can last for up to 7 days. The half-life of procalcitonin is about 20–35 hours after the loss of inflammatory signals, such as bacterial endotoxin. Procalcitonin is degraded by proteolysis and a small portion is excreted through the kidneys [7,9]. The biological function of PCT itself is still unclear; it has been reported that PCT has pro and anti-inflammatory properties. The immunological role of PCT may be a cofactor that can modulate the impact of shock from endotoxins. PCT regulates in response to pro-inflammatory mediators, such as IL-1 $\beta$ , TNF- $\alpha$ , and IL-6. Some studies show that serum procalcitonin decreases against cytokines (such as interferon-gamma) released during viral infections [9].

PCT was first discovered as an additional biomarker that was useful for guiding sepsis in 2006 where PCT acted as a good diagnostic marker for sepsis, severe sepsis, and septic shock. In an analysis of 30 studies, Wacker et al. [11] found that high PCT levels did indeed indicate sepsis, and low PCT levels had to prevent the initiation of antibiotics. However, they cannot recommend specific cut off, and PCT levels must be interpreted in a clinical context [11]. A more recent meta-analysis defines a certain threshold level of 0.5 mg/dl, and finds that it is most useful and accurate in diagnosing sepsis in ICU patients, but worst in immunocompromised patients. They recommend that low PCT levels should help to exclude bacteremia [12].

PCT levels can increase in certain situations without infection. For example, in conditions of prolonged or severe cardiogenic shock, anaphylactic, prolonged and prolonged organ perfusion anomalies, small cell lung cancer or thyroid medullary C-cell carcinoma, early after major trauma, major surgical intervention, severe burns, and in neonates ( $<48$  hours after birth). PCT may also fail in the initial phase of infection [13]. It was recently reported that the diagnostic accuracy of PCT in patients with acute kidney injury is lower than in patients without acute renal failure (ARF) because PCT is eliminated through the kidneys and/or liver. PCT levels were found to be higher in patients with infection with ARF, but an increase in PCT levels in ARF patients was (at least partially) related to the severity of infection and kidney dysfunction. The diagnostic accuracy of PCT for infections in patients with ARF is not lower than in patients without ARF. PCT is a useful marker of bacterial infection in

patients with AKI, but a different cut-off must be applied [14]. A study conducted by Svaldi et al. [15] on 475 research samples, states that the condition of hematological diseases that have severe leukopenia and immunocompromise can affect PCT levels, with positive predictive value (cut-off 2 ng/ml) and negative predictive value (cut-off) 0.5 ng/ml) PCT for sepsis is 93% and 90% in patients with leukocyte counts  $> 1,000/\text{mm}^3$ , 66% and 63% in leukopenia conditions.

PCT is measured with immunoassay technique and all tests were standardized using the original Brahms PCT luminescence immunoassay. Currently, PCT rapid test measurement with Brahms PCT-Q has also been developed using lateral flow immunochromatography which produces reddish or brown color bands, classified into four PCT levels ( $<0.5$ ; 0.5–2.0; 2.0–10;  $> 10$  ng/ml) [8,16].

Our study compared two PCT measurement methods. The first is the FREN<sup>TM</sup> PCT FIA method and the second is the Elecsys BRAHMS PCT Cobas e411 Roche autoanalyzer ECLIA method. We used serum samples from 99 newly diagnosed sepsis patients. The Wilcoxon test shows that there is no significant difference in PCT concentration measured between the two methods. There is a strong correlation (Spearman's  $r = 0.941$ ,  $p < 0.0001$ ) between the results of procalcitonin in both methods. In addition, a categorical comparative test with McNemar's test on the sample is also performed, the results obtained in the form of numbers into the sepsis category or not.

However, the comparative regression line between the two methods shows a difference, this is seen at higher PCT concentrations, but not at the lower end, where the medical cut-off is located. Current literature supports that PCT thresholds  $\geq 0.5$  and  $\geq 2.0$  ng/ml to detect the possibility of sepsis, and PCT  $\geq 10$  ng/ml indicate a high likelihood of severe sepsis or septic shock [8,16]. Furthermore, in the PCT diagnostic test, the FIA method using the ROC curve showed an AUC result of 0.62 ( $p = 0.0075$ ), with a sensitivity of 82.35% and a specificity of 41.67%. Whereas in the PCT diagnostic test the ECLIA method using the ROC curve showed almost the same results, AUC of 0.61 ( $p = 0.01$ ), with a sensitivity of 80.39% and specificity of 41.67%. There are some discrepancies between procalcitonin results in comparison to the SOFA scores (36%) and PELOD-2 scores (40%) in both methods. This might be due to data limitations that affect the calculation of the PELOD-2 score.

## Conclusion and Limitations

The conclusion of this study is the examination of procalcitonin by the FIA (FREN<sup>TM</sup> PCT) method has many advantages, which include portability, more affordable cost, comfort, and relatively fast results so that it can be used in health facilities in remote areas that do not have an analyzer for sepsis detection. This method has a strong correlation and is not significantly different from the ECLIA method (Cobas e411), especially in adult patients. Its usage in pediatric patients requires further research.



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# Guidelines for transplant patients during the COVID-19 pandemic

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**Objective:** The causative agent of COVID-19 is highly contagious because it is spread both through direct respiratory droplets and through objects and direct contact, and one patient can infect about 3 people. Patients who had undergone transplantation are susceptible to many infections, including COVID-19. Therefore, this group of patients is considered a risk group and requires a high level of preventive measures. There is no extensive experience and science-based action plan in this field, and most of the recommendations are based on expert opinions and small-size experiences. The following recommendations can be made taking into account surveys, expert opinions and small-size experiences conducted by leading international transplant communities (TTS, ILTS, ESOT, ASOT, EASL, etc.).

**Keywords:** transplantaion, COVID-19.

## Strictly follow the general measures

Transplant patients must strictly follow the general measures applied in the region (personal hygiene, social isolation). All personal hygiene items should be kept separate, houses should be ventilated periodically, and a distance should be kept from family members, especially those who go out.

## Establish remote communication (telemedicine)

During this period, it is recommended that physician-patient communication be performed through video communication technologies in order to reduce the number of patients coming to hospitals and spread of infection.

## Decentralization

It is recommended that patients living far from transplant centers to have tests and necessary examinations at their place of residence, and that clinical examinations be performed by local physicians if necessary. It is also important to establish coordination between transplantologists and local doctors.

## Change immunosuppression only when indicated

It is not recommended to change immunosuppressive regimens due to the risk of COVID-19. It is recommended to continue standart immunosuppression as before. Immunosuppressive regimens can be changed in consultation with a transplantologist only in special circumstances:

- in case of serious side effects related to drugs - leukopenia, lymphopenia,
- If there are superinfections
- When certain drugs are used in COVID-19 patients.

## Interventions and invasive examinations should be performed only in emergency cases

It is recommended to delay routine examinations, especially invasive examinations and interventions (endoscopy, ERCP), as much as possible. It is recommended to perform them only in emergency cases (bleeding, cholangitis, stricture, etc.)

### Living donor transplant operations

It is recommended to postpone elective transplantation. In emergency transplantation, it is recommended to examine both the recipient and the donor for COVID-19, to obtain an informed consent regarding high risks and to perform operation in hospitals isolated from COVID-19 patients.

### Indications for hospitalization

Transplant patients are recommended to be hospitalized only with emergency indications.

### Guidelines for transplant patients with confirmed COVID-19 infection

Transplant patients with suspected COVID-19 infection should be tested immediately. If COVID-19 is confirmed, pa-

tients should be hospitalized and receive treatment. Paracetamol is recommended as a non-steroid in transplant patients, especially in liver transplant patients, and the dose should not exceed 2-3 g/day. Interactions with immunosuppressive drugs should be considered during COVID-19 treatment. (Table 1). Because most of these drugs interact with calcineurin and m-TOR inhibitors, blood levels of immunosuppressants should be monitored periodically.

### References

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**Table 1.** Interaction of drugs used in COVID-19 with immunosuppressive drugs.

| Drug name                                     | Interaction  |
|---|--|
| Remdesivir (antiviral)                        | Interaction with immunosuppressive drugs is unknown. Immunosuppressive drug levels need to be monitored.   |
| Chloroquine/hydroxychloroquine (anti-malaria) | Has drug interaction with tacrolimus, cyclosporine and m-TOR inhibitors. Immunosuppressive drug levels need to be monitored.                                 |
| Lopinavir / ritonavir (antiviral)             | Has drug interaction with immunosuppressants. Should not be used in combination with m-TOR inhibitors. Tacrolimus, cyclosporine levels need to be monitored. |
| Tocilizumab (anti-IL-6)                       | Interaction with immunosuppressants is unknown. Immunosuppressive drug levels need to be monitored.  |
| Umifenovir (Arbidol) (antiviral)              | May interact with immunosuppressive drugs. Immunosuppressant levels need to be monitored.  |
| Favipiravir / favilavir (antiviral)           | May interact with immunosuppressive drugs. Immunosuppressive drug levels need to be monitored.   |
| Sofosbuvir (antiviral)                        | It can be used with immunosuppressive drugs, there is no need to change the dose.  |





# Hemolytic Uremic Syndrome Still Confuses Minds: A Case With All Three Components of the Triad

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**Abstract:** Hemolytic uremic syndrome (HUS) is a condition that presents with a triad of microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure. It is one of the leading causes of acute renal failure in the pediatric population. Its etiology includes infection, systemic diseases and various other causes. Prognosis depends on immediately starting plasmapheresis and if necessary, eculizumab. We report a patient that was admitted with bloody diarrhea and presented with all three components of the triad. The patient's renal function normalized after treatment with plasmapheresis and hemodialysis.

**Keywords:** Hemolytic uremic syndrome; hemolytic anemia; thrombocytopenia; acute renal failure.

## Introduction

Hemolytic uremic syndrome (HUS) is a condition that presents with microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure. In HUS, clinical signs begin after thrombotic microangiopathy. Pathologic lesions are artery and capillary wall thickening as well as endothelial thickening and damage. Thrombi made up of fibrin and thrombocytes can block arteries, leading to multiple organ damage including the kidneys. HUS is one of the leading causes of acute renal failure in the pediatric population. It must be considered in the differential diagnosis of children with anemia, decreased urine output and hematologic issues secondary to a recent viral infection and diarrhea. It is important to rule out thrombotic thrombocytopenic purpura (TTP) in the differential diagnosis of HUS based on ADAMTS 13 activity, which tends to be low in TTP.

## Case Report

A 12-year-old female was referred to our clinic with complaints of sharp abdominal pain and bloody diarrhea for 10 days, and no urine output for 4 days. On day 3 after the

complaints started, the family had applied to a different clinic and outpatient treatment was started. On day 3 of treatment, urine output began to decrease, and hemodialysis was started 2 days before the patient was referred to our clinic. At the same time, the patient's mother and grandmother were being treated for bloody diarrhea at the first clinic at the same time.

On admission, the patient was conscious, weak and in respiratory distress with accessory muscle use. Skin and mucous membranes were pale. On auscultation, the patient had dyspnea and wet fine crackles; heart sounds were muffled. Abdominal palpation showed sharp pain, liver and spleen could not be palpated. Laboratory findings were as follows: WBC 11.700 /mm<sup>3</sup>, HGB 5.7 g/dL, PLT 33.000/mm<sup>3</sup>, creatinine 4.4 mg/dL, urea 95 mg/dl, BUN 44mg/dl, LDH 2125 U/L, total bilirubin 1.29 mg/dl, direct bilirubin 0.6mg/dl, direct Coombs negative, complement C3 1.13 g/l, complement C4 0.23g/l. Urinalysis showed 3+ blood and 3+ protein. Stool analysis showed high amounts of mucus, leukocytes and erythrocytes. Stool culture revealed no pathogenic bacteria (antibiotic treatment had been started at the previous clinic). Abdominal USG showed

intestinal wall inflammation and signs of grade 1 bilateral renal parenchymal disease; kidney size was normal. Liver and spleen echogenicity and size were normal.

The triad of hemolytic anemia, thrombocytopenia and acute renal failure pointed to the diagnosis of hemolytic uremic syndrome. Plasmapheresis and hemodialysis were started. Due to respiratory distress, the patient was placed on mechanical ventilation. After 3 days, the patient was extubated. On day 10 of treatment urine output started to improve, and on day 16 output normalized and treatment was stopped. Laboratory findings were normal: WBC 4.590/mm<sup>3</sup>, HGB 10.9 g/dl, PLT 179.000/mm<sup>3</sup>, creatinine 1.1mg/dl, urea 38.9 mg/dl, BUN 17mg/dl. The patient was discharged on day 22 and remains on outpatient follow-up with no problems.

### Discussion

HUS is the leading cause of acute renal failure in children and is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia and acute renal damage. It is often observed after upper respiratory tract infections and gastroenteritis. The two types of HUS are diarrhea-positive (typical) and non-diarrhea-associated (atypical). Typical HUS is most often caused by *E.coli* O157:H7 as well as streptococcus pneumoniae, HIV and various other infections. Among the genetic causes of HUS are mutations in genes of the complement system, cobalamin C metabolism deficiency and DGKE gene mutations. In cases of atypical HUS, genetic testing is recommended in addition to first line treatment of plasmapheresis and eculizumab when necessary. If a genetic mutation is confirmed and renal failure progresses to the final stage, a renal transplant is recommended.

Diagnostically HUS is characterized by spherocytes and schistocytes in peripheral blood smear, anemia, thrombocy-

topenia, reticulocytosis, azotemia, elevated LDH and indirect bilirubin, and low haptoglobin.

The symptomatic approach to HUS includes red blood cell transfusion if HGB is 6-7 g/dL or hematocrit is <18%. Thrombocyte transfusions are necessary in cases of clinically significant hemorrhage or during invasive procedures. Other measures include maintaining daily fluid volume, correcting electrolyte imbalances, stopping medications that are nephrotoxic or implicated in HUS etiology, and providing normal nutrition.

Prognosis in hemolytic uremic syndrome depends on timely treatment; recovery follows in 90% of cases. Lasting complications can develop as a result of microthrombosis of various organs.

### Conclusion

It is a fact that hemolytic uremic syndrome in children and infants may not be diagnosed easily and quickly. The main safeguard against mortality and morbidity remains a high index of suspicion.

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# WMA International Code of Medical Ethics

*Adopted by the 3<sup>rd</sup> General Assembly of the World Medical Association, London, England, October 1949 and amended by the 22<sup>nd</sup> World Medical Assembly, Sydney, Australia, August 1968 and the 35<sup>th</sup> World Medical Assembly, Venice, Italy, October 1983 and the 57<sup>th</sup> WMA General Assembly, Pilanesberg, South Africa, October 2006.*

## **DUTIES OF PHYSICIANS IN GENERAL**

A PHYSICIAN SHALL always exercise his/her independent professional judgment and maintain the highest standards of professional conduct.

A PHYSICIAN SHALL respect a competent patient's right to accept or refuse treatment.

A PHYSICIAN SHALL not allow his/her judgment to be influenced by personal profit or unfair discrimination.

A PHYSICIAN SHALL be dedicated to providing competent medical service in full professional and moral independence, with compassion and respect for human dignity.

A PHYSICIAN SHALL deal honestly with patients and colleagues, and report to the appropriate authorities those physicians who practice unethically or incompetently or who engage in fraud or deception.

A PHYSICIAN SHALL not receive any financial benefits or other incentives solely for referring patients or prescribing specific products.

A PHYSICIAN SHALL respect the rights and preferences of patients, colleagues, and other health professionals.

A PHYSICIAN SHALL recognize his/her important role in educating the public but should use due caution in divulging discoveries or new techniques or treatment through non-professional channels.

A PHYSICIAN SHALL certify only that which he/she has personally verified.

A PHYSICIAN SHALL strive to use health care resources in the best way to benefit patients and their community.

A PHYSICIAN SHALL seek appropriate care and attention if he/she suffers from mental or physical illness.

A PHYSICIAN SHALL respect the local and national codes of ethics.

## **DUTIES OF PHYSICIANS TO PATIENTS**

A PHYSICIAN SHALL always bear in mind the obligation to respect human life.

A PHYSICIAN SHALL act in the patient's best interest when providing medical care.

A PHYSICIAN SHALL owe his/her patients complete loyalty and all the scientific resources available to him/her. Whenever an examination or treatment is beyond the physician's capacity, he/she should consult with or refer to another physician who has the necessary ability.

A PHYSICIAN SHALL respect a patient's right to confidentiality. It is ethical to disclose confidential information when the patient consents to it or when there is a real and imminent threat of harm to the patient or to others and this threat can be only removed by a breach of confidentiality.

A PHYSICIAN SHALL give emergency care as a humanitarian duty unless he/she is assured that others are willing and able to give such care.

A PHYSICIAN SHALL in situations when he/she is acting for a third party, ensure that the patient has full knowledge of that situation.

A PHYSICIAN SHALL not enter into a sexual relationship with his/her current patient or into any other abusive or exploitative relationship.

## **DUTIES OF PHYSICIANS TO COLLEAGUES**

A PHYSICIAN SHALL behave towards colleagues as he/she would have them behave towards him/her.

A PHYSICIAN SHALL NOT undermine the patient-physician relationship of colleagues in order to attract patients.

A PHYSICIAN SHALL when medically necessary, communicate with colleagues who are involved in the care of the same patient. This communication should respect patient confidentiality and be confined to necessary information.



# Azerbaijan Medical Association

## ABOUT

The Azerbaijan Medical Association (AzMA) is the country's leading voluntary, independent, non-governmental, professional membership medical organization for physicians, residents and medical students who represent all medical specialties in Azerbaijan.

Association was founded by Dr. Nariman Safarli and his colleagues in 1999. At the founding meeting, the physicians adopted the Statutes and Code of Ethics of the Association. The AzMA was officially registered by Ministry of Justice of Azerbaijan Republic in December 22, 1999.

***Since its inception, the AzMA continues serving for a singular purpose: to advance healthcare in Azerbaijan.***

- Founded in 1999, the AzMA provides a way for members of the medical profession to unite and act on matters affecting public health and the practice of medicine.
- We are the voice of physicians who support the need for organized medicine and want to be active within their profession.
- We are the representative for Azerbaijan doctors on the world-wide level and the voice of Azeri physicians throughout the world.

## MISSION

The mission of the Azerbaijan Medical Association -is to unite all members of the medical profession, to serve as the premier advocate for its members and their patients, to promote the science of medicine and to advance healthcare in Azerbaijan.

## GOALS

- Protect the integrity, independence, professional interests and rights of the members;
- Promote high standards in medical education and ethics;
- Promote laws and regulation that protect and enhance the physician-patient relationship;
- Improve access and delivery of quality medical care;
- Promote and advance ethical behavior by the medical profession;
- Support members in their scientific and public activities;
- Promote and coordinate the activity of member-specialty societies and sections;
- Represent members' professional interests at national and international level;
- Create relationship with other international medical associations;
- Increase health awareness of the population.

***The association's vision for the future, and all its goals and objectives are intended to support the principles and ideals of the AzMA's mission.***

## INTERNATIONAL RELATIONSHIPS

Since its establishment, AzMA built close relationships with many international medical organizations and national medical associations of more than 80 countries. The following are the AzMA's international affiliations:

- Full membership in the World Medical Associations (WMA) (since 2002)
- Full membership in the European Forum of Medical Associations (EFMA) (since 2000)
- Full membership in the Federation of Islamic Medical Associations (FIMA) (since 2002)
- Associate membership in the European Union of Medical Specialists (UEMS) (since 2002)

Especially the year 2002 remained with memorable and historical events for AzMA such as membership to the World Medical Association (WMA). Today we are extremely pleased to represent our Association and to be a part of the WMA family.

## MEMBERSHIP

A person with medical background, who accepts and follows the AzMA Statutes and AzMA Code of Ethics, may become a member of the Association. The Code of Ethics of the Association shall be the members' guide to professional conduct.

Membership in the AzMA is open to:

- Physicians residing and practicing in Azerbaijan and in abroad.
- Medical students enrolled at medical universities or schools
- Retired physicians

Members can access a special members only area of the AzMA website designed to provide the most up-to-date, and timely information about organized medicine in our country.

To the non-member, we hope you'll discover, through our website how valuable Azerbaijan Medical Association is to medicine in Azerbaijan and will join us.

## MEDICINE'S VOICE IN AZERBAIJAN

As the largest physician membership organization in Azerbaijan the AzMA devotes itself to representing the interests of physicians, protecting the quality of patient care and as an indispensable association of busy professionals, speaks out with a clear and unified voice to inform the general public and be heard in the highest councils of government.

The AzMA strives to serve as the Medicine's Voice in Azerbaijan.

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For more information, please visit our website:  
[www.azmed.az](http://www.azmed.az)

for notes

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**We work together for the  
sake of healthy future of  
Azerbaijan!**



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