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RESEARCH ARTICLE

ROLE OF IVERMECTIN, DOXYCYCLINE ALONG WITH SUPPORTIVE CARE IN TREATMENT OF COVID-19 POSITIVE CHILDREN (>9 YEAR) AND ADOLESCENT AGE GROUP" A PROSPECTIVE OBSERVATIONAL STUDY FROM TERTIARY CARE CENTER OF WESTERN U.P"

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Abstract

Background: In December 2019, the infection caused by 2019 novel coronavirus led to an outbreak in Wuhan, situated in the Hubei Province of China. The number of studies on children with COVID-19 is limited. We reviewed that COVID-19 does indeed affect children the same way as any other age group. Children can act as carriers of the virus and can endanger the lives of other individuals.

Aim: In this Prospective study a combination of Ivermectin, Doxycycline along with supportive care was evaluated therapeutically to treat COVID-19 children (> 9 year) and adolescent age group.

Method: Study was performed on pediatric COVID-19 patient who were enrolled in this study with a predefined inclusion and exclusion criteria. RT- PCR of the SERS-CoV-2 was done. The clinical features and response to treatment were noted according to protocol. Patients were divided in 2 groups.Combination of Ivermectin, Doxycycline and supportive treatment were given in one group and other group acted as control. Retesting was done between 5 to 25 days of starting medication.

Result: In the study after excluding 50 patients, out of remaining 110 patients, males and females were 67 and 43 respectively, the age ranged between 9-18 years (Mean age was 10.88 ± 2.39 year). Retesting was done between 5 to 25 days of starting medication. Symptomatic improvement was noticed after 2-3 days of starting medication. Mean recovery time in Ivermectin-Doxycycline-supportive care group (Group B) was 10.28±4.72 versus 14.92±8.40 in control group. Hence, using Ivermectin along with Doxycycline reduced mean time to recovery up to 4.64 days. By analyzing the mean time to recovery in mild, moderate and severe patients in each group, it was shown that the mean time to recovery in Group B was 6.88±1.84,11.78±1.81, 21.28±1.79 days, respectively vs 8.375±1.25, 12.76±1.73, 23.16±1.47 days respectively in Group A. All patients symptomatically improved and tested negative. No death was noted in either group.

Conclusion: Most of the cases of SARS-CoV-2 were mild and did not require specific treatment but combination of Ivermectin and

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Doxycycline along with supportive care was found to be effective in early viral clearance and helped the patients to overcome the disease early. Early improvement of symptoms and early discharge were noted in patients whom we gave combination of medicines. Over all it is a very cheap combination, save a lot of lives, and very helpful for resource-poor settings. This study has limitations as our number of patients was small.

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Introduction:-

Global health care systems are facing the arduous challenges of this unknown disease, which has drastically attacked human society. This new pathogen, as well as severe acute respiratory syndrome (SARS) coronavirus and Middle East respiratory distress syndrome (MERS) coronavirus, belong to b-type coronaviruses but have different genetic characteristics .[1]Although some studies have indicated a wild-animal origin, the origin of SARS-CoV-2 is still unclear .[2]

In the beginning of April 2020, Caly et al. from Monash University, Australia published their research article stating that a single dose of Ivermectin (an anti-parasitic drug) could decrease the concentration of coronavirus in vitro. In the lab, Caly et al. noted 93-99.8% reduction in viral RNA for Ivermectin versus DMSO control at 24h in the supernatant (released virions) and cell associated viral RNA (total virus) respectively. They also described by 48 hours about 5000-fold reduction of viral RNA and maintenance of effect at 72 hours.[3]

Doxycycline is rapidly and almost completely absorbed after oral administration and has half-life of 16-18 hours. Based on the available evidence, we believe Tetracyclines may be effective agent in the treatment of Covid-19 due to their ability to chelate Zinc compounds on matrix metalloproteinases (MMP) on which coronaviruses rely heavily for survival, cell infiltration, cell to cell adhesion and replication. It is a safe and inexpensive drug with a minimal toxicity.[4]

Methodology:-

Study design:
Prospective Observational study

Study Population:
All RT-PCR SARS- CoV-2 positive children fulfilling the selection criteria. Mild to moderate COVID-19 positive pediatric patients from tertiary care center of Western U.P

Study period:
April 2020 –April 2021

Inclusion Criteria:
Patients age group 9 to 18 years, with either sex, male or female, confirmed cases of Covid-19 by RT-PCR test or COVID antigen positive, Patients not critically ill or on immunosuppressive drug, Patients who were classified as asymptomatic, Mild and moderate cases, Severe cases with typical symptoms, Patients who were not already treated with any other antiviral drug.

Exclusion criteria:
Patients who were very severe and critically ill or patients who needed ventilatory support, Age less than 9 year and weight less than 20 kg, Age more than 18 years, Children with chronic illness, Patients with inadequate data, Immunocompromised, Cancer patients, and on other antiviral drugs.

Procedure:
160 patients (RT-PCR confirmed cases) of SARS CoV-2 met the selection criteria and were enrolled in the study. In the study after excluding 50 patients on the basis of exclusion criteria, out of remaining 110 patients, male and

female were 67 and 43 respectively, the age ranged between 9-18 years. RT- PCR of the SERS-CoV-2 was done. The clinical features and response to treatment were noted according to protocol. RT-PCR test was repeated with sample of nasal swab for all patients according to availability of testing centers between 5 to 25 days. Six weeks after testing negative, we planned to follow up on the patients about their health conditions.

Randomization and Intervention:
For study patients were divided into 2 groups as follow:
Group A (n=40) - Supportive treatment was given to this group of pediatric patients (control group)
Group B(n=70) - Ivermectin, Doxycycline along with supportive treatment was given to this group of patients.

The dose of Ivermectin was 0.2mg/kg for 3-5 days according to severity of symptoms in children 9-12 years of age and 0.2-0.4 mg/kg for 3-5 days in children more than 12 years according to severity of symptoms. Dose of Doxycycline was 100 mg every 12 hours on first day, then 100 mg once a day for 7-10 days in children more than 45 kg body weight and 4.4 mg per kg of body weight divided into 2 doses on first day, then 2.2 mg per kg of body weight per day single or 2 divided doses for 7-10 days according to severity of symptoms in children less than 45 kg body weight.

All the subjects were provided with symptomatic treatment for mild and moderate symptoms of COVID-19. The schedule of medication intake was explained to patient's attendant for pediatric patient who were less than 12-year-old and to the patients who were more than 12-year-old. Instruction included that Ivermectin tab to be taken on an empty stomach 1 hour before meal. Doxycycline capsule to be taken twice daily after meal for 10 days starting from day 1.

The randomization process as well as the patients records for disease progression, recovery, and clinical or laboratory testing were supervised.

Repeat Nasopharyngeal and throat swab PCR:
PCR Retesting was done between 5 to 25 days of starting medication. End points were a negative PCR and resolution of symptoms. The duration from the first day of drug intake to the negative PCR was counted as the Recovery Period.

Data analysis:
Data was processed according to the normality tests results; parametric data were represented with mean values and non-parametric data were represented with median values. Mean age of infection was calculated in both groups. Percentage of recovery and mortality rate was calculated for each group of the study. Mean duration of recovery was compared in both groups. Data evaluated on the basis of mean, median, standard deviation, percentage.

Result:-

out of total 160 patients, 50 Patients were excluded on the basis of exclusion criteria (3 needed ventilatory support, 6 were suffering from chronic illness, 15 adequate data not available, 18 were less than 9-year-old, 8 were more than 9 years but less than 25 kg weight.

This observational study, consisting of 67 males and 43 females was conducted from April 2020 to April 2021 in a tertiary care center of western U.P. The oldest patient was 18 years and the youngest one was 9 years.

In main Study group (Group B)- Ivermectin, Doxycycline and supportive treatment was given.

In Control group (Group A): The patients in this group received only supportive care (Placebo) which included all or some of the following, according to the clinical condition of each patient.

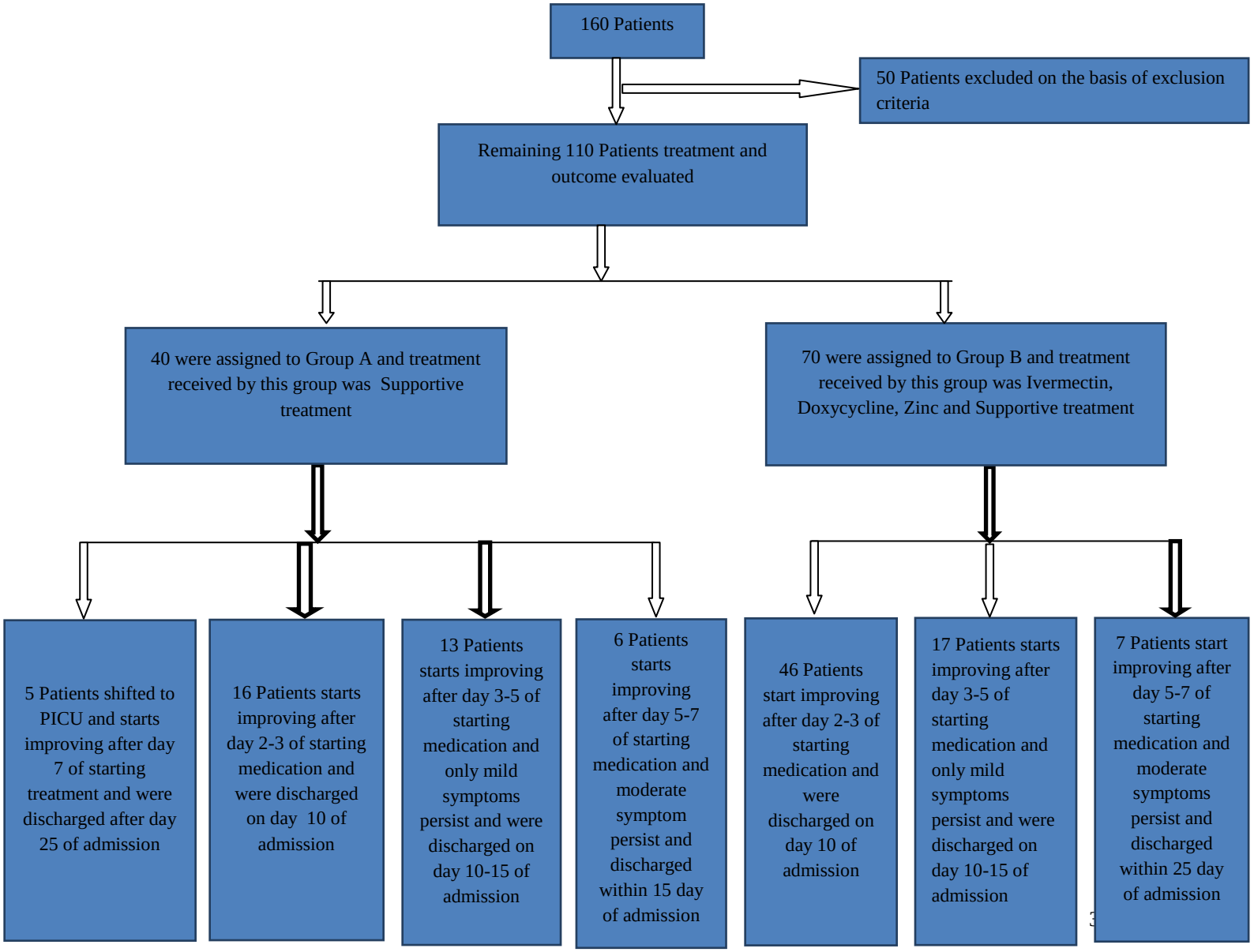
Placebo therapy (supportive care as per standard protocol) - Azithromycin, Acetaminophen, Vitamin C, Zinc, Vitamin D3, Steroids and oxygen therapy, metered dose inhaler if needed according were given according to protocol.

Mean age of the recruited patients was 10.88 ± 2.39 years with range 9-18 years. Patients in both groups were age- and sex- matched.

Mean age of Group B was 10.87± 2.29 years with 46 (65%) males and 22(31.4%) females while mean age of control group (Group A) patients was 10.9±2.58 years with 21 (52.5%) males and 19 (47.5%) females. In both groups, the median post-infection day for starting therapy was 2-3 days in mild, 3-5 days in moderate, 5-7 days in severe cases.

Table1:- Baseline characteristics of study group patients.

Age (Total)	Age (Group B)	Age (Group A i.e., control group)
Total Patients=110 Age group=9-18 years Male=67(60.9%) Female=43(39.09%) Mean age =10.88 year SD=2.39 Min. Age 9 year (36.36%pt belong to this age) Max. Age 18 year	Total patient in this group =70 Age group = 9-18 years Male = 46(65%) Female=22(31.4%) Mean age=10.87 year SD=2.29 Min. Age 9 year (35.71% pt. belong to this age) Max. Age 18 year	Total patient in this group=40 Age group=9-18 years Male=21(52.5%) Female=19(47.5%) Mean age 10.9 year SD=2.58 Min. Age 9 year (37.5% pt. belong to this age) Max. age 18 year



51(16+35) patients tested negative with in 10 days of illness. 41(13+28) patients tested negative with in 10-15 days of illness. 13(6+7) patients tested negative with in 25 days of illness. All of the patients tested negative with in 10-25 days. 5 patients shifted to PICU and discharged after day 25. No death was reported.

In Group B, 35(50%) Patients started improving after day 2-3 of starting treatment and were discharged within day 10 of admission whereas in Group A 16(40%) Patients start improving after day 2-3 of starting medication.
In Group B 28(40%) Patients start improving after day 3-5 of starting medication and only mild symptoms persist and were discharged on day 10-15 of admission whereas in Group A, 13 (32.5%) patients started improving after day 3-5 of starting medication.In Group B, no Patient needed PICU admission while in Group A, 5 Patients needed PICU admission.

Both Groups has 100% recovery but duration of recovery was more in Group A, while mean recovery duration was shorter in Group B. Randomized treatment study group A and B the presenting symptoms of the covid 19 were fever, cough, fatigue, dyspnea, chest pain, diarrhea, myalgia and abdominal pain.

Mean recovery time in Group B was 10.28±4.72 days versus 14.92±8.40 days in control group. Hence, using Ivermectin along with Doxycycline reduced overall mean time to recovery up to 4.64 days. By analyzing the mean time to recovery in each group, it was shown that the mean time to recovery for mild, moderate and severe cases in Group B was 6.88±1.84, 11.78±1.81, 21.28±1.79 days, respectively versus 8.375±1.25, 12.76±1.73, 23.16±1.47days in control group, respectively. Accordingly, Ivermectin-Doxycycline along with supportive care reduced recovery time by about 1.49 days (roughly 1.5 days) in mild, and 0.98 day (or roughly 1 day) in moderate and 1.88 days (or roughly 2 days) in severe patients.

	Group B (cases=70)	Group A (control group n=40)	Reduction in recovery time and outcome
Total (n=110)	Size n=70 cases Max time of recovery =25 days Minimum time of recovery =5 days Mean = 10.28 days Median = 10 days Mode= 10 days SD= 4.72	Size n=40 cases Max time of recovery 40 days. Minimum time of recovery = 7 days. Mean= 14.925 days Median=13 days Mode=10 days SD=8.40	Ivermectinand Doxycycline combination reduces mean time of recovery by up to 4.64 days.
Mild	Size n=35 cases Max time of recovery=10 days Min. time of recovery=5 days Mean=6.88 days Median=6 days Mode =5 days SD=1.84	Size n-=16 cases Max. Time of recovery =10 days Min. Time of recovery=7 days Mean=8.375 days Median=8.5 days Mode =7 days SD=1.25	Ivermectin and Doxycycline combination reduces mean time of recovery by up to roughly 1.5 days.
Moderate	Size n= 28 cases Min. Time of recovery=10 days Max. Time of recovery= 15 days Mean=11.78 days Median =11 days Mode =10 days SD=1.81	Size n= 13 cases Min. Time of recovery=10 days Max. Time of recovery=15 days Mean=12.76 days Median=13 days Mode=13 days SD=1.73	Ivermectin and Doxycycline combination reduces mean time of recovery by up to roughly 1 day as compared to control group.

Severe	Size n=7 cases Min. Time of recovery=20 days Max. Time of recovery=25 days Mean=21.28 days Median=21 days Mode=20 days SD=1.799	Size n=6 cases Min. Time of recovery=21 days Max. Time of recovery=25 days Mean=23.16 days Median=23.5 days Mode= 24 days SD=1.47	Ivermectin and Doxycycline combination reduces mean time of recovery up to roughly 2 days
Critical cases	No case shifted to PICU	5 cases shifted to PICU but all recovered Min. Time of recovery=25 days Max. Time of recovery=40 days Mean=31.6 days Median=30 days SD=5.94	No death recorded

Table 2: - Time of recovery.

Out of 40 COVID-19 patients in control group, 5(12.5%) cases progressed to more advanced stage of the disease, being classified as critical cases, while no patient need critical care support in Group B (ivermectin and Doxycycline-supportive care group). Thus, Ivermectin-Doxycycline protocol were lower the progression of the disease in severe patients if given within the first two to three days of the severe stage of the disease. The mortality rate was shown to be 0/48 (0%) in mild-moderate patients in both groups.

Discussion:-

Ivermectin is a relatively safe and well-tolerated anti-parasitic drug for head lice, scabies, onchocerciasis, and strongyloidiasis and acts by inhibiting nuclear transport activity.[5] In-vitro studies have shown its function against human immunodeficiency virus (HIV), dengue, influenza, and most recently, against SARS-CoV-2. This effectiveness against SARS-CoV-2 infection is due to its critical interaction with RNA viruses responsible for integrase protein nuclear import.[6,7] A recent report suggests that Ivermectin reduces mortality rates in hospitalized patients with COVID-19.[8] However, it is not known if antiviral levels are attainable while using known dosing regimens of Ivermectin therapy in patients with COVID-19.[9,10] Thus, it is vital to investigate the dose regimens of Ivermectin for COVID-19 treatment and to determine if there is appropriate synergism using combination therapy with another drug.

Doxycycline is in the tetracycline class of antibiotics that acts via the inhibition of bacterial ribosomes. Itis a well-tolerated bacteriostatic drug that has a long history of clinical use.[11] The efficacy and tolerability of Ivermectin and Doxycycline in combination were established in an earlier study for the treatment of onchocerciasis.[12] Several recent studies have suggested a therapeutic role of Doxycycline against COVID-19.[13,14] Our study suggests in mild, moderate and severe patients the Ivermectin-Doxycycline combination expressed an earlier and faster relief from COVID-19 as compared to control group with supportive care alone.

Ivermectin and Doxycycline were used in this study because both drugs have shown antiviral and immunomodulatory activities .[15-22] The findings of the current trial showed that Ivermectin-Doxycycline reduced the mean time to recovery from 14.92 to 10.28 days in the recruited COVID-19 patients. Alike, for mild patients, Ivermectin-Doxycycline reduced mean time to recovery from 8.37 to just 6.88 days with reduction in time up to 1.5 days roughly. And for moderate patients from 12.76 days to 11.78 days with reduction in time up to 1 day roughly. Ivermectin-Doxycycline reduced the mean time to recovery in severe patients by only 2 days, from 23.16 to 21.28 days. Based on these findings, Ivermectin and Doxycycline protocol proves to be effective in speeding up recovery in mild, moderate and severe inpatients. This may have a tremendous effect on lowering the burden of the disease, minimizing chances of developing immune deregulation, and freeing as quickly as possible hospital beds to other patients. This study adds further evidence that Ivermectin-Doxycycline could exert both antiviral and immunomodulatory actives.

Several observational studies showed that Ivermectin with/without Doxycycline shortens the time needed to recovery of COVID-19 patients and Ivermectin is beneficial for mild-moderate as well as severe patients.[15-22] In the current study, Ivermectin-Doxycycline arm lowered the rate of progression of disease. Out of 40 COVID-19 patients in control 5 (12.5%) cases (these 5 cases were not from mild to moderate group) progressed to more advanced stage of the disease,being classified as critical cases, while no patient needed critical care support in Group B (ivermectin and Doxycycline group). Thus, Ivermectin-Doxycycline protocol was shown to lower progression of the disease in severe patients if given within the first two to three days of the severe stage of the disease.

Accordingly, the present clinical trial reveals that Ivermectin-Doxycycline combination might slow the disease progression and reduce death rate in severe patients of COVID-19. An observational preprint study conducted in Florida showed that Ivermectin cuts mortality rate of severe COVID-19 patients from 80.7% to 38.8%.[23] Interestingly, both Ivermectin and Doxycycline concentrations in the tissue of the lung have been estimated 2 times more than that in plasma .[24,25] Therefore, their antiviral and anti-inflammatory effect on pulmonary tissues is expected to be prominent.

Doxycycline is largely excreted unchanged both in the bile and urine and the dose does not require adjustment in patients with renal failure, Because of the enterohepatic circulation this drug may remain in the body for a long time after cessation of therapy. Doxycycline can produce GI irritation most commonly after oral administration. Tolerability can be improved by administering it with food. Doxycycline can be safely used in children aged 8 years and above.[26]

Limitations of study;
This study includes relatively small sample size, Case selection and also the outcome may be biased by additional factors like severity of the disease, lack of cooperation.

Conclusion:-

From our study, we conclude that most of the cases of SARS-CoV-2 were mild and did not require specific treatment but combination of Ivermectin and Doxycycline along with supportive care was found to be effective in early viral clearance, and shorten recovery duration. This combination of medicines helps the patients to overcome the disease early. The present clinical study reveals that Ivermectin-Doxycycline along with supportive care might stop disease progression if used in the first few days of being positive with or without symptoms may reduce unnecessary deaths. We can also stop the community transmission by asymptomatic carriers by treating the asymptomatic COVID-19 positive patients. Early improvement of symptoms and early discharge was seen in patients whom we gave combination of medicines. Above all it is a very cheap combination, and can save a lot of lives, especially beneficial for resource-poor settings. This study has limitations as our number of patients was small; Further study is required on a larger scale.

Abbreviations
COVID-19-Coronavirus disease 2019
RT PCR-Real-time Polymerase Chain Reaction
SERS-CoV-2- severe acute respiratory syndrome coronavirus 2
MMP- matrix metalloproteinases

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