

Original Article

Clinical Characteristics and Outcomes of Paediatric Non-tuberculous Mycobacterial Infection: Single Institution Retrospective Review Over Past 20 Years

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Abstract

Non-tuberculous mycobacterial (NTM) infection is uncommon yet clinically significant as it could cause severe morbidity and mortality. This study reviewed all paediatric patients under 20 years of age diagnosed to have NTM infection in Queen Mary Hospital during 1 January 1999 to 30 June 2018. Total 7 patients were identified with median age of diagnosis at 6 years old and median duration of follow up for 30 months. Majority (86%) have underlying comorbidities such as haemic malignancies or history of stem cell transplantation. Clinical manifestations varied from lymphadenitis, pulmonary infection, osteomyelitis, arthritis to systemic bacteraemia. Infective agents include *Mycobacterium fortuitum*, *M. abscessus* and *M. chelonae*. Mortality rate was high (29%). High index of suspicion and early recognition of NTM infection is important especially in immunocompromised and at-risk individuals. Prompt administration of appropriate therapy improves patient outcomes. Multidisciplinary collaboration is crucial. Treatment could be difficult and prolonged. Drug-related toxicities are common.

Key words

Diagnosis; Morbidity; Nontuberculous mycobacteria; Therapeutics

Introduction

Non-tuberculous mycobacteria (NTM) are ubiquitous in the environment such as water, soil, dust, animals, and birds. By far, more than 190 species of NTM have been

identified, and approximately 60 of which are suspected or known to be pathogenic in humans. Despite of their low virulence and indolent clinical course of infection, NTM infection could cause severe morbidity and mortality. Clinicians should not overlook this group of relatively less common yet clinically significant infection, especially in oncology and transplant settings. Retrospective review on clinical data helps summarise experience and remind physicians not to overlook this possibility especially in susceptible group of patients.

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Methods

Study Design

A single-centre retrospective study was conducted in the University Department of Paediatrics and Adolescent Medicine of Queen Mary Hospital (QMH), a university-affiliated hospital offering tertiary and quaternary clinical services with encounter of highly complex patients in daily practice. All patients under 20 years of age and diagnosed to have NTM infection in QMH during 1st January 1999 to 30th June 2018 were retrieved through Clinical Data

Analysis and Reporting System using the diagnostic code (ICD-9) for "non-tuberculous mycobacterial infection" (031.9). Information on patient demographics, presence of underlying co-morbidities, clinical manifestations of infection, duration between symptom onset and confirmation of laboratory diagnosis, infective agent identified, sensitivity pattern, treatment given and duration, presence of complications as well as final outcome were collected and studied from written and electronic medical records through the Clinical Management System. All clinical isolates were sent to the Department of Health Public Health Laboratory Service Branch Centre for Health Protection for identification and susceptibility testing under standard broth dilution method and interpreted according to the Clinical and Laboratory Standards Institute. Patients without definitive diagnosis of NTM infection were excluded from the study. BCGiosis and immune reconstitution inflammatory syndrome (IRIS) due to Bacille Calmette-Guérin (BCG) strain of *Mycobacterium bovis* were excluded as *M. bovis* is considered part of *M. tuberculosis* complex (MTBC). MPT64 antigen detection in culture isolates were performed to exclude MTBC from genuine NTM infections.

Statistical Analyses

This study was primarily descriptive in nature.

Continuous variables were expressed as median and range. Duration of follow up was defined from the date of first clinical presentation or diagnosis to date of last follow up (censorship) or death.

Ethical Considerations

This study complies with the Declaration of Helsinki and approval from Institutional Review Board of the University of Hong Kong / Hospital Authority Hong Kong West Cluster had been obtained (UW 18-597 / HKUCTR-2581).

Results

Patient Demographics (see Table 1)

Total 7 patients with genuine NTM infection were identified (3 males, 4 females) with median age at diagnosis of 6 years old (range 4-20 years old) and median duration of follow up of 30 months (range 3 days up to 120 months). Majority (86%, 6 out of 7) have underlying comorbidities, such as haemic malignancies or post-stem cell transplantation (n=4), autoimmune diseases or immunodeficiency (n=1) and chronic respiratory disease (n=1). Clinical manifestations include systemic bacteraemia (n=3), lymphadenitis (n=2), osteomyelitis or

Table 1 Case series of paediatric non-tuberculous mycobacterial infection in Queen Mary Hospital over past 20 years (1999-2018)

No	Agent	Sex	Age at diagnosis	Time from symptom onset to confirmed	Co-morbid laboratory disease diagnosis	Site of infection	Status	Duration of follow up
1	<i>M. fortuitum</i>	F	5 years	3 months	APECED	Lymphadenitis	Dead	18 months
2	<i>M. chelonae</i>	M	20 years	2 months	AML M2 t(6;9) MUD PBSCT gut GVHD, BO	Pneumonia and bacteraemia	Dead	2 months
3	<i>M. chelonae</i>	M	4 years	1 month	JMML, NF-1	Central line infection and arthritis	Alive	120 months
4	<i>M. fortuitum</i>	F	17 years	1 month	Beta-thal major post MUD PBSCT severe GVHD	Pneumonia and bacteraemia	Dead	5 months
5	<i>M. abscessus</i> <i>subsp. massiliense</i>	M	6 years	1 month	Cystic fibrosis	Pneumonia	Alive	82 months
6	<i>M. abscessus</i> <i>subsp. abscessus</i>	F	4 years	1 month	AML t(8;21)	Right groin, popliteal, ankle osteomyelitis and subcutaneous abscesses	Alive	30 months
7	<i>M. abscessus</i> <i>subsp. abscessus</i>	F	11 years	1 month	Nil	Left submandibular lymphadenitis	Alive	30 months

AML: acute myeloid leukaemia; APECED: autoimmune polyendocrinopathy with candidiasis and ectodermal dysplasia; BO: bronchiolitis obliterans; F: female; GVHD: graft-versus-host disease; HLA: human leukocyte antigen; JIA: juvenile idiopathic arthritis; JMML: juvenile myelomonocytic leukaemia; M: male; M.: mycobacterium; MUD: matched unrelated donor; NA: not applicable; NF: neurofibromatosis; PBSCT: peripheral blood stem cell transplant; t: translocation, thal: thalassaemia

arthritis (n=2), and pulmonary infection (n=2). Median time from symptom onset to confirmation of laboratory diagnosis is 1 month.

Microbiology (see Table 2)

Infective agents identified including *M. abscessus complex* (n=3) (*M. abscessus subsp. abscessus* =2, *M. abscessus subsp. massiliense* =1), *M. fortuitum* (n=2), and *M. chelonae* (n=2). In general, the mycobacteria identified were sensitive to amikacin, showing intermediate sensitivity to cefoxitin, linezolid and meropenem; variable sensitivity to clarithromycin, levofloxacin, linezolid and cotrimoxazole; and resistant to ciprofloxacin, doxycycline and moxifloxacin. Mortality rate was up to 29% (2 out of 7 died).

Treatment and Related Toxicities (see Table 3)

For the 2 patients with pneumonia and systemic bacteraemia due to mycobacteria, both died before treatments were completed, the one with *M. chelonae* infection (Case 2) was treated with intravenous (IV) imipenem-cilastatin with oral clarithromycin while the other with *M. fortuitum* infection (Case 4) was treated with IV imipenem-cilastatin with amikacin for 3 weeks during intensive phase followed by oral levofloxacin as continuation therapy (planned for 6 months but was given for around 5 months then patient died of progressive respiratory failure).

For the 2 patients with lymphadenitis, the one with *M. fortuitum* lymphadenitis (Case 1) was cured with 6 months of IV meropenem and amikacin while the other patient with *M. abscessus* lymphadenitis (Case 7) was treated with IV amikacin and cefoxitin/tigecycline for 4

weeks as initial treatment followed by oral clarithromycin for 4 months in total as maintenance therapy.

For the patient with central line infection due to *M. chelonae* (Case 3), prompt removal of central line followed by treatment with triple agents (IV imipenem-cilastatin, IV amikacin and oral clarithromycin) suffices to eradicate the catheter-related mycobacterial infection.

The patient with cystic fibrosis with pneumonia due to *M. massiliense* (Case 5) was treated according to United Kingdom Royal Brompton Hospital clinical guideline for the care of children with cystic fibrosis 2011 with 3-week intensive phase of IV amikacin, IV meropenem, IV cefoxitin and oral clarithromycin followed by prolonged continuation phase with nebulised amikacin and oral azithromycin daily for 1 year then continued with oral azithromycin 3 day per week for 2 more years for anti-inflammatory effect.

For the remaining patient with right groin, popliteal, ankle osteomyelitis and subcutaneous abscesses (Case 6), initial treatment was failed with 2-month course of oral clarithromycin, three 2-week courses of IV amikacin, 2 weeks of IV levofloxacin, 1 month of IV imipenem-cilastatin, 2 weeks of IV cefoxitin, and 1-month course of interferon-gamma (3 days per week). The patient was successfully salvaged with 2 re-purposed drugs (oral bedaquiline and clofazimine) together with cotrimoxazole.

Drug-related toxicities were encountered in 3 out of the 7 patients treated (Cases 5-7), and all manifested as drug fever and fixed drug eruptions - 2 due to the beta-lactam cefoxitin (Cases 5, 6) while 1 due to cotrimoxazole (Case 7). One also developed hepatitis (Case 6) with alanine transaminase and aspartate transaminase elevated above 1,000 requiring discontinuation of all anti-mycobacterial

Table 2 Sensitivity patterns of non-tuberculous mycobacteria cultured from affected paediatric patients in Queen Mary Hospital (1999-2018)

No	Amikacin	Cefoxitin	Ciprofloxacin	Clarithromycin	Doxycycline	Levofloxacin	Moxifloxacin	Linezolid	Cotrimoxazole	Imipenem
<i>M. fortuitum</i>										
1	S	I		I	R	S				S
4	S	I		R	R	S				
<i>M. chelonae</i>										
2	S				R					
3	S	S		S	R	R	R	S		
<i>M. abscessus complex (including subsp. abscessus and massiliense)</i>										
5	S	I	R	S	R		R	I	R	I
6	S	I	R	R	R		R	S	S	I
7	S	I	R	S	R		R	I	S	R

I: intermediate; R: resistant; S: sensitive

Table 3 Treatment regime, duration and related toxicities

No	Agent	Site(s) of infection	Initial treatment (intensive phase)	Maintenance treatment (prolonged continuation phase)	Treatment-related toxicities and final outcome
1	<i>M. fortuitum</i>	Lymphadenitis	(1) IV meropenem 350 mg q12h (20 mg/kg/dose) for 6 months (2) IV amikacin 250 mg q24h (15 mg/kg/dose) for 6 months	Nil	Cured (patient died 18 months later due to sepsis and multi-organ failure unrelated to episode of mycobacterial infection)
2	<i>M. chelonae</i> / <i>abscessus</i> complex	Pneumonia and bacteraemia	(1) IV imipenem-cilastatin 500 mg q6h (15 mg/kg/dose)* (2) Oral azithromycin 500mg daily (15 mg/kg/day) p.o.*	Not applicable	Died due to progressive respiratory failure
3	<i>M. chelonae</i> / <i>abscessus</i> complex	Central line related infection and arthritis	Removal of central line (1) IV imipenem-cilastatin q6h (15 mg/kg/dose) for 3 weeks (2) IV amikacin (15 mg/kg/day) q24h for 3 weeks (3) Oral clarithromycin 500 mg BD p.o. for 3 weeks	Nil	Cured
4	<i>M. fortuitum</i>	Pneumonia and bacteraemia	(1) IV imipenem-cilastatin 500 mg q6h (15 mg/kg/dose) for 3 weeks (2) IV amikacin 500 mg (15 mg/kg/day) q24h for 3 weeks	Levofloxacin 250 mg daily p.o. (8 mg/kg/day) (plan for 6 months, given for around 5 months then patient died)	Died due to progressive respiratory failure
5	<i>M. abscessus</i> complex (<i>subsp. Massiliense</i>)	Pneumonia	(1) Amikacin 7.5 mg/kg b.d. for 3 weeks (2) Meropenem 40 mg/kg max. 2 gm t.d.s. IV for 3 weeks (3) Cefoxitin 200 mg/kg/day IV in 3-4 divided doses for 3 weeks (4) Clarithromycin 500 mg b.d. p.o. for 3 weeks	(1) Nebulised amikacin 250 mg b.d. given for 1 year (2) Azithromycin [^] 175 mg (10 mg/kg) daily for 1 year then switched to 3 times per week for anti-inflammatory effect, continued for 2 more years then self-stopped	Cured Developed drug fever and fixed drug eruptions (likely due to cefoxitin or meropenem), also developed hepatitis

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Table 3 Treatment regime, duration and related toxicities (cont'd)

No	Agent	Site(s) of infection	Initial treatment (intensive phase)	Maintenance treatment (prolonged continuation phase)	Treatment-related toxicities and final outcome
6 ²⁸	<i>M. abscessus</i>	Right groin, popliteal and ankle osteomyelitis with subcutaneous abscesses	Radical surgical debridement with insertion of antibiotics-infused cement (1) Oral clarithromycin for 2 months (2) Cotrimoxazole 480 mg BD p.o. (trimethoprim 10 mg/kg/day) for 2 months (3) IV amikacin 15 mg/kg/day q24h for 2 weeks per cycle for 3 cycles in total (as prolonged amikacin would result in irreversible ototoxicity) (4) IV levofloxacin for 2 weeks then IV imipenem-cilastatin for 1 month then IV ceftiofur 200 mg/kg/day for 2 weeks, stopped due to drug rash and hepatitis (5) Interferon-gamma for 1 month (3 days per week)	(1) Bedaquiline 100 mg daily p.o. daily for 1 month then daily (3 days per week) (2) Clofazimine 50 mg daily p.o. for 1 month then daily (2 days per week) (3) Cotrimoxazole 480 mg BD p.o. (trimethoprim 10 mg/kg/day)	Developed drug rash and hepatitis likely due to ceftiofur, stopped IV ceftiofur (also oral clarithromycin and cotrimoxazole), rash subsided and liver function normalised in 1 week Given total 8 months of bedaquiline and clofazimine. Infection treated and limb function preserved.
7	<i>M. abscessus</i>	Left submandibular lymphadenitis	(1) Oral clarithromycin 375 mg b.d. for 4 weeks (2) Oral levofloxacin 375 mg daily p.o. (given for 4 days) Switched to IV ceftiofur 1.45 gm q6h (40 mg/kg/dose) based on sensitivity (given for 5 days), further switched to oral cotrimoxazole 480 mg b.d. (given for 12 days then developed fever, rash and leukopenia), then switched to IV tigecycline 50 mg q24h (1.5 mg/kg/day) and given for 2 weeks (3) IV amikacin 540 mg (15 mg/kg/day) q24h for 4 weeks - withheld for 3 days when developed side effects due to cotrimoxazole, switched to IV imipenem-cilastatin 500 mg q6h (15 mg/kg/dose)	Oral clarithromycin 375 mg BD for 4 months (counted from initiation of treatment)	Developed fever, rash and leukopenia after given oral cotrimoxazole for 12 days Cured

b.d.: bis die sumendum (two times a day); gm: gram(s); IV: intravenous; kg: kilogram(s); M.: mycobacterium; max.: maximum; mg: milligram(s); p.o.: per os (by mouth); q6/12/24h: every 6/12/24 hours; t.d.s.: ter die sumendum (three times a day)

* Treatment not completed as patient died of progressive respiratory failure. Patient also on concurrent IV micafungin 100 mg q24h (3 mg/kg/day) and IV ambisome 100 mg q24h (3 mg/kg/day) for aspergillus pneumonia

^ Azithromycin was chosen instead of clarithromycin as less chance of macrolide resistance as compared to clarithromycin

agents for 1 week before resuming antimicrobials when liver function normalised.

Discussion

Classification of Mycobacteria

Mycobacteria are aerobic acid-fast bacilli under genus Actinobacteria. Over 190 species had been identified so far, and approximately 60 of which are suspected or known to be pathogenic in humans. NTM refer to mycobacteria apart from MTBC, *M. leprae* and *M. ulcerans*. Distinguishing NTM from MTBC is of clinical significance as rapidly-growing NTM are in general not susceptible in vitro to anti-TB drugs but susceptible to traditional bactericidal agents. Besides, TB is a notifiable disease requiring public health tracking while NTM is not on the contrary. NTM comprises mycobacteria in environment which are non-pathogenic and also NTM which may cause diseases in humans.^{1,2} NTM could be categorised by Runyon's classification into photochromogens, scotochromogens, non-chromogens (such as Mycobacterium avium complex MAC) and rapid growers known as rapidly growing mycobacteria (RGM)³ (such as *M. abscessus*, *M. fortuitum* and *M. chelonae*). RGM are environmental organisms found worldwide that typically grow within 1 week in suitable culture medium. Potential diagnostic limitations in distinguishing different species occur and different susceptibility patterns for different species.⁴

Clinical Manifestations of NTM Infections

Clinical syndromes caused by NTM include pulmonary disease^{5,6} (Cases 2, 4 and 5), lymphadenitis^{7,8} (either localised cervical lymphadenitis or complicated disseminated lymphadenitis) (Cases 1 and 7), skin and soft tissue infections⁹ (either superficial chronic cutaneous lesions or deep-seated infections involving tendons, synovium, bones and joints) (Case 6), intra-vascular catheter related infections¹⁰⁻¹³ and/or systemic bacteraemia (Cases 2, 3 and 4) as well as continuous ambulatory peritoneal dialysis-related peritonitis.¹⁴ For local case cohort, we encountered almost all different clinical manifestations as stated above.

Immunity Against Mycobacterial Infection

Cell-mediated immunity is the major protective immune response against intracellular bacteria, with non-tuberculous mycobacteria being one of them.^{15,16} Th1

lymphocytes can produce interferon-gamma (IFN- γ) which activates macrophage to kill phagocytised intracellular microbe. In local cohort, one of the cases (Case 6) had incorporated IFN- γ as part of anti-mycobacterial treatment.

Risk Factors for Development of NTM Infections

Steroid and cytotoxic therapy predispose to a wide combination of phagocytic, cell-mediated and even humoral defects.^{9,17} From local case series, 6 out of 7 have underlying acquired or congenital immunodeficiency render them predispose to non-tuberculous mycobacterial infection, with underlying haemic malignancies or history of stem cell transplantation being the commonest group (n=4), reflecting usage of steroid and/or cytotoxic therapy being an important risk factor for development of NTM infections.

Consideration of Primary Immunodeficiency in Patients with NTM Infections

Among the 7 cases in local cohort, one (Case 7) of them was with good past health and no underlying comorbidities, it is postulated that subtle immune defect could exist and investigations on Mendelian susceptibility to mycobacterial diseases (MSMD) are under way though not yet revealing at the time of publication.

Diagnosis and Treatment

Despite knowing the importance in differentiating TB and NTM, as mentioned they are in practical not easily distinguishable from clinical history, Mantoux test result, radiological pattern and initial laboratory reports. They also share overlapping clinical features such as pulmonary disease and lymphadenopathies. Delayed in diagnosis is common. The disease burden of NTM is unknown in region such as Hong Kong where TB is endemic. As no mandatory reporting is required, epidemiology and clinical studies are scarce. NTM are often assumed to be TB and treated as such, but susceptibility to antimicrobials are in fact very different. Classical anti-TB drugs (streptomycin, isoniazid, rifampicin, pyrazinamide and ethambutol) (S, H, R, E, Z) are generally not useful because of intrinsic resistance.^{18,19}

Treatment against NTM differs in different patients according to the clinical manifestations, type of mycobacteria identified, sensitivity pattern, underlying comorbidities and the presence of drug-related toxicities.²⁰⁻²² Surgical debridement²³ (Case 6) or removal of foreign body (such as central venous

catheter) (Case 3) are indicated in selected cases.²⁰⁻²² Anti-mycobacterial treatment is usually prolonged in terms of months or years with employment of multiple antimicrobial agents in an attempt to avoid development of drug resistance.²⁰⁻²² Amikacin, imipenem, cefoxitin, clarithromycin and azithromycin are the key drugs commonly used to treat NTM infections.^{20-22,24} From the sensitivity patterns of local cohort, NTM isolated are generally sensitive to amikacin; demonstrated intermediate sensitivity to cefoxitin, linezolid and meropenem; variable sensitivity to clarithromycin, levofloxacin, linezolid and cotrimoxazole; and resistant to ciprofloxacin, doxycycline and moxifloxacin (see Table 3). Development of multiple-drug resistant (MDR) strains of mycobacteria as well as compliance and drug-related toxicities related to prolonged duration of treatment are the 2 major challenges faced by physicians in combating NTM infections.

Macrolide Resistance

Macrolide resistance for NTM, in particular *M. abscessus* spp. *abscessus* and *bolletii* exists due to erm gene. Macrolide resistance is associated with delayed treatment response and possible treatment failure in patient with lung disease on macrolide-containing regimens.²⁵ However, including a macrolide (clarithromycin or azithromycin) in the multidrug regimen may still be considered in such situations as the choice of oral alternatives is limited. Thus, macrolide was incorporated as part of treatment regime for the 3 local cases with *M. abscessus* infection (Cases 5-7) (including Case 5 which later identified to be *M. massiliense*).

Drug-related Toxicities (see Supplementary Table 3)

From literature review, around 7% patients would develop adverse drug reactions towards anti-TB/NTM treatment, with transaminitis/ hepatotoxicity being commonest (87%), followed by rash (8%), angioedema (5%) and gastrointestinal intolerance.²⁶ Combination therapy is associated with increased toxicity.²⁶ Treatment time is on average being prolonged by a median of 1 month due to ADR.²⁶ In our study, drug-related toxicities were encountered in 3 out of the 7 patients treated (43%) (Cases 5-7), and all manifested as drug fever and fixed drug eruptions. Hepatotoxicity is encountered in 1 patient only (Case 6) with anti-NTM treatment withheld for 1 week.

Novel Treatment Agents

For Case 6 who was a 4-year old girl with translocation t (8;21) acute myeloid leukaemia who developed right

groin, popliteal, ankle osteomyelitis and subcutaneous abscesses due to *M. abscessus* after 2 courses of induction chemotherapy, 2 experimental drugs (bedaquiline and clofazimine) were used to salvage this patient as off-label use in view of treatment failure against traditional anti-NTM agents. Bedaquiline and clofazimine are agents to treat MDR-TB and leprosy in adults, with uncertain efficacy in paediatric population. Both are lipophilic agents and able to achieve high bactericidal concentrations in soft tissues. Disease control had been achieved in this patient.²⁸

Besides antimicrobial agents, 2 agents were also considered in the same patient to enhance patient's own cellular immunity against NTM infection, namely pegylated granulocyte colony-stimulating factor (pegfilgrastim) and IFN- γ . Pegfilgrastim administration was associated with a significant increase of the inducible IL-12p40 subunit in patient serum.²⁷ Whereas in patients given filgrastim with a much shorter half-life of around 3.5-3.8 hours as compared to 42 hours for pegfilgrastim, IL-12p40 slightly declined and returned to baseline values by day +11 from the commencement of cytokine treatment. It is tempting to speculate that immunoreactive IL-12 in patients given filgrastim may have been degraded as a result of sharp increases in circulating PMN capable of releasing proteolytic enzymes. Side effect profile of pegfilgrastim is similar to filgrastim.

Strengths and Limitations of Study

This is the first study reporting patient characteristics, microbiology, treatment and outcomes of paediatric NTM infections in QMH over past 20 years. Despite the very small number of cases extracted from local cohort of a single paediatric department which makes it difficult to draw definitive conclusions or generalise the findings, this paper crystallises experience and serves as a timely reminder to paediatric oncologists and transplant physicians not to overlook possibility of NTM infections in their specific clinical settings with common encounter of immunocompromised children facing the conglomeration of all five local paediatric oncology centres into single paediatric oncology and transplant centre at Hong Kong Children's Hospital since 2019. In addition, it also enlightens general paediatricians, immunologists and infectious disease specialists to look for concealed immunodeficiencies for children presented with NTM infections without know underlying susceptibility conditions. In the future, a territory-wide study or international collaboration with inclusion of adult cases would be recommended.

Conclusion

To conclude, anticipation and early recognition of NTM infections especially in immunocompromised patients is important to facilitate prompt provision of appropriate therapy to improve clinical outcomes. Concealed immunodeficiencies should be actively sought for in children presented with NTM infections without known underlying susceptibility conditions. Multidisciplinary collaboration is crucial. Treatment could be difficult and prolonged and drug-related toxicities are common.

Declaration of Interest

None

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