2021 WHO Expert Committee on Selection and Use of Essential Medicines

Proposal for the inclusion of ampicillin and gentamicin on the EMLc for the new indication of complicated intra-abdominal infections in neonates and children

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1. Summary statement of the proposal for inclusion, change or deletion.

This application concerns the updating of the forthcoming WHO Model List of Essential Medicines for Children (EMLc) to add an indication for antibiotics already listed in the EMLc. In particular, this application concerns the addition of complicated intra-abdominal infections as a new indication for ampicillin and gentamicin. The indication applies to both mild and severe infections.

This application proposes an amendment to the complementary list in section *6.2.1 Access group antibiotics* as per the latest edition of the core EMLc (7th edition, 2019). This application is not proposing to add any new medicines to the EMLc but only to include an additional indication to already listed medicines.

The main reason for the addition of a new indication for these antibiotics is to align the EMLc with current WHO guidelines, in particular with the Pocket book of hospital care for children (2nd edition, 2013) (1). Ampicillin in combination with gentamicin and metronidazole is recommended for the empiric treatment of community-acquired complicated intra-abdominal infections in neonates and children. The Pocket book of hospital care for children recommends this combination of three antibiotics in several chapters dedicated to intra-abdominal infections (e.g. chapter on appendicitis, bowel obstruction in neonates, incarcerated hernia, abdominal wall defects). Metronidazole is already included on the EMLc for this indication.

We report here below other relevant documents and recommendations that support the request for inclusion of ampicillin in combination with gentamicin and metronidazole for the treatment of community-acquired complicated intra-abdominal infections in neonates and children.

Relevant supporting documents:

- The Review of Antibacterial Medicines for the WHO Model List of Essential Medicines 2017 Update carried out by the Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton Canada (see Appendix).
    - Authors reported that the review of systematic reviews yielded indeterminate results, therefore recommendations for the EML (including for children) were based on the review of national and international guidelines. In particular, two guidelines informed the EML recommendations, and these were 1) the 2010 Infectious Diseases Society of America (IDSA) / Surgical Infection Society (SIS) guidelines (2) and 2) the guidelines developed at the 2010 consensus conference of the World Society of Emergency Surgery (WSES) (3).
    - The authors summarized the IDSA guidelines for children as follows: "For community acquired infection in children, **the recommendations are aminoglycoside-based regimens (gentamicin or tobramycin in combination with metronidazole or clindamycin with or without ampicillin)**, a carbapenem (ertapenem, meropenem, imipenem), a beta-lactam/beta-lactamase inhibitor combination (piperacillin-tazobactam, ticarcillin-clavulanate), or advanced-generation cephalosporins (cefotaxime, ceftriaxone, ceftazidime, cefepime) plus metronidazole. With severe beta-lactam allergies, either an aminoglycoside or ciprofloxacin plus metronidazole are recommended".
        - Additionally (but this was not part of the McMaster review since it was published after the review took place) in 2017 the Surgical Infection Society revised the 2010 guidelines (4) and confirmed aminoglycosides-based regimens for neonates, in particular the guidelines say "**Use ampicillin, gentamicin, and either metronidazole** or clindamycin; ampicillin, cefotaxime, and either

metronidazole or clindamycin; or meropenem **in pediatric patients less than one month** of age (45 weeks post-conceptional age)".

- In the WSES guidelines, pediatric treatment is not specifically addressed.

- The 2017 WHO recommendations on newborn health (5):
  - In this case the guideline specifically addresses the empiric antibiotic treatment of **necrotizing enterocolitis** in neonates and recommends the use of **ampicillin in combination with gentamicin (without metronidazole)** for 10 days which is the same empiric treatment recommended in the same guideline for neonatal sepsis.

2. Relevant WHO technical department and focal point (if applicable).
Maternal, Newborn, Child & Adolescent Health & Ageing

3. Name of organization(s) consulted and/or supporting the application.
McMaster University in Hamilton, Canada has collaborated in the preparation of this application.

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

INN	**ATC**
Ampicillin	J01CA01
Gentamicin	J01GB03

5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).
Dose forms and strengths as currently listed on the EMLc.

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.
The application is to add an indication to ampicillin and gentamicin as individual medicines (metronidazole is already listed for this indication).

Treatment details, public health relevance and evidence appraisal and synthesis
7. Treatment details (requirements for diagnosis, treatment and monitoring).
Proposed dose and duration for the empiric treatment of intra-abdominal infections in neonates and children is:

Ampicillin (IV/IM):
- 50 mg/kg per dose, twice a day (1st week of life for those born at 35 weeks or more)
- 50 mg/kg per dose, three times a day (>1st week of life)

AND
Gentamicin (IV/IM):
- Neonates: 5 mg/kg /dose given once a day
- Children: 7.5 mg/kg/dose given once a day

AND
Metronidazole:
- Neonates: 7.5 mg/kg per dose, twice per day
- Children: 7.5 mg/kg per dose, three times per day

Treatment duration is 4-7 days unless source control has not been achieved and/or the patient is not improving clinically.

Information supporting the public health relevance.

Epidemiological information on disease burden

Community-acquired intraabdominal infections occur in children worldwide and are caused by a variety of conditions most frequently acute appendicitis and in endemic settings intestinal perforation occurring as a complication of enteric fever (6). Acute appendicitis is particularly frequent in children and most cases (70%) are uncomplicated and with a very low short-term post appendectomy mortality (1%) (7). However, variation across settings in the incidence of new cases exists and while a decrease has been observed in western Europe and North America since the 1990s, increasing trends are reported in Asia, South America and the Middle East (8).

Assessment of current use

Table 1 reports **what is currently recommended** in the EMLc for the empiric treatment of community-acquired intra-abdominal infections

Table 1 Recommendations for the empiric treatment of community-acquired complicated intra-abdominal infections in children

Severity	Antibiotic options and doses
Mild cases The proposed change would add an additional second choice option for the treatment of mild cases	***First choice*** Amoxicillin–clavulanic acid (IV): 40-50 mg/kg per dose of amoxicillin component, twice a day OR Ceftriaxone (IV): 50-100 mg/kg per dose, once a day or Cefotaxime (IV): 50mg/kg per dose, three times per day AND Metronidazole (IV): • Neonates: 7.5 mg/kg per dose, twice a day • Children: 7.5 mg/kg per dose, three times per day ***Second choice*** Ciprofloxacin (oral): 10-15 mg/kg per dose, twice per day AND Metronidazole (oral): • Neonates: 7.5 mg/kg per dose, twice a day • Children: 7.5 mg/kg per dose, three times per day OR Ampicillin AND Gentamicin AND Metronidazole (doses indicated in section 7)
Severe cases The proposed change would add an additional second choice option for the treatment of severe cases	***First choice*** Piperacillin– tazobactam (IV): 100 mg/kg per dose of piperacillin component, three times per day ***Second choice*** Meropenem(IV): 20 mg/kg per dose, three times per day OR Ampicillin AND Gentamicin AND Metronidazole (doses indicated in section 7)

Mild cases are defined as patients who are not critically ill, with no suspicion of sepsis or septic shock. Severe cases are defined as patients who are critically ill, with suspicion of sepsis or septic shock.

Target population
Neonates and children diagnosed with complicated intra-abdominal infections.

Likely impact on the burden of disease
It is unlikely that the proposed addition has an impact on the burden of disease per se.

9. Review of benefits: summary of evidence of comparative effectiveness.

These antibiotics are commonly used in neonates and children and are already listed in the EMLc for other indications and the evidence of benefits (and harms and toxicity) has already been extensively revised by the EML Working Group and Expert Committee.
In particular ampicillin is already listed in the EMLc as first choice for the treatment of severe community acquired pneumonia, complicated severe acute malnutrition and sepsis (in neonates and children). Ampicillin is also listed as second choice for the treatment of acute bacterial meningitis.
Gentamicin is already listed in the EMLc as first choice for the treatment of severe community acquired pneumonia, complicated severe acute malnutrition and sepsis (in neonates and children). Gentamicin is also listed as second choice for surgical prophylaxis.

Additionally, in the Review of Antibacterial Medicines for the WHO EML 2017 Update carried out by the Department of Health Research Methods, Evidence, and Impact of the McMaster University, aminoglycosides had been listed for this indication as targeted antibiotics based on local resistance data as alternative options to the core antibiotics and regarding ampicillin it was reported that it can be considered if additional enterococcal coverage is needed if the used regimen would otherwise not be covering *Enterococcus* (e.g. ceftriaxone/metronidazole).

These antibiotics are commonly used in children for complicated intra-abdominal infections and available worldwide and no additional evidence discouraging their use has occurred since the Review of Antibacterial Medicines for the WHO EML 2017 Update.

10. Review of harms and toxicity: summary of evidence of safety.
The same considerations mentioned above in the section “review of benefits” are applicable to harms and toxicity.

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.
As the proposed medicines are already included on the Model Lists and in many national essential medicine lists, a review of the comparative costs and cost-effectiveness has not been undertaken.

Regulatory information
12. Summary of regulatory status and market availability of the medicine.
Ampicillin and gentamicin have regulatory approval globally and are available as generics.

13. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia).
Ampicillin and gentamicin are listed in multiple pharmacopoeias including the United States Pharmacopeia and European Pharmacopoeia.

14. References

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5. Geneva: World Health Organization. WHO recommendations on newborn health: guidelines approved by the WHO Guidelines Review Committee 2017 [Available from: https://apps.who.int/iris/handle/10665/259269.
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Appendix

Relevant extract from the Review of Antibacterial Medicines for the WHO Model List of Essential Medicines 2017 Update by the Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton Canada

Complicated intra-abdominal infections.

The full Review is available at:
https://www.who.int/selection_medicines/committees/expert/21/applications/comprehensive_antibiotics_rev/en/

Complicated Intrabdominal infections

Complicated intra-abdominal infection (cIAI) are infections that extend beyond the viscus of origin into the peritoneal space and are associated with either peritonitis or abscess formation. They represent a diverse group of infections for which there are a broad spectrum of causative agents, although Streptococci, Enterobacteriaciae and anerobes predominate. We are not considering primary peritonitis, from hematogenous dissemination (e.g. spontaneous bacterial peritonitis in the absence of an underlying infection of the viscus), usually in the setting of an immunocompromised state, or dialysis-related infections.

Synopsis of published evidence

We retrieved 27 systematic reviews with quality scores ranging from 50-72, with most in the low to low/moderate category. Although we retrieved reviews for treatment of peritoneal dialysis-associated peritonitis, prophylaxis, and antibiotic treatment versus surgery for uncomplicated acute appendicitis, we will not consider these as the focus was therapy for complicated intra-abdominal infection with secondary peritonitis. A total of 5 systematic reviews were included as relevant for the scope of this work[151-156].

In a 2005 review[156], 40 studies (5,094 patients) were evaluated to compare the efficacy of various antibiotics for secondary peritonitis, i.e. infection of the visceral organ that extend beyond the organ, e.g. complicated appendicitis or cholecystitis. 38 of the 40 studies compared two regimens of antibiotics and 2 studies compared 3 regimens. The antibiotics evaluated included carbapenems (meropenem or imipenem), as single agents compared to each other or to cephalosporin and metronidazole combination or to pipercillin-tazobactam, regimens of clindamycin and an aminoglycoside (gentamicin or amikacin or tobramycin) compared to pipercillin-tazobactam. The trials were non-inferiority and all showed similar efficacy and no differences in mortality.

There were no differences in overall mortality or mortality due to infection when aminoglycoside and anerobic regimens were compared to others with very large confidence intervals, though: OR 2.03, 95% CI 0.88 to 4.71 and OR 1.51, 95% CI 0.66- 3.43 respectively. However, aminoglycoside-based regimens were shown to be inferior against all comparators available in terms of clinical success (OR 0.65, 95% CI 0.46-0.92).When broad spectrum beta-lactams were compared to other regimens, there were no significant differences in infection related mortality (OR 0.54, 95% CI 0.05-6.08) or in clinical cure (OR 1.22, 95% CI 0.56, 2.66). When carbapenems were compared to others, there was no significant difference in infection related mortality (OR 0.78, 95% CI 0.30-2.03) or clinical cure (OR 0.71, 95% CI 0.47-1.07). For cephalosporins alone versus other agents,

there was no difference in infection related death (OR 0.63, 95% CI 0.10-3.84) nor for clinical success (OR 1.25, 95% CI 0.57-2.74). Similarly for cephalosporin and anti-anaerobe regimens versus others, no difference in infection related death (OR 5.45, 95% CI 0.25-116.63) nor for clinical success (OR 0.71, 95% CI 0.29 to 1.75) was observed. However, the group of cephalosporins and beta-lactams were found to be superior in terms of clinical success compared to all other comparators (OR 3.21, 95% CI 1.49-6.92), as were fluoroquinolones combined with an anti-anaerobic agent (OR 1.74, 95% CI 1.11-2.73). As no specific antibiotic groups had been compared to one specific other antibiotic group, no firm conclusions can be drawn from this evidence. It is possible that an outlier antibiotic group (e.g. aminoglycoside-based antibiotics as in Wong et al.[156]) was driving the inferiority of the comparator group, while other groups within the comparator group could have been non-inferior or even superior to beta-lactam.

In a systematic review and meta-analysis comparing ertapenem to ceftriaxone (eight RCTs, 2,883 patients), similar clinical success was reported OR 1.13, 95% CI 0.75 to 1.71.[152] A comparison of moxifloxacin to other antibiotics (4 RCTs, 2,444 patients), showed similar effects for clinical cure (OR 0.80, 95% CI 0.61-1.04) and mortality (OR 0.91, 95% CI 0.45-1.83); more adverse events were observed in the moxifloxacin group (OR 1.33, 95% CI 1.07-1.63), however, the overall incidence of serious adverse events was similar (OR 1.23, 95% CI 0.59-2.60).[154]

A review comparing ertapenem to pipercillin-tazabactam (6 RCTs, 3,161 patients) showed no difference in clinical success (OR 1.15, 95% CI 0.89-1.49).[151] In an older systematic review[153], ciprofloxacin plus metronidazole was found to be superior in terms of clinical cure than beta-lactam based antibiotics (OR 1.69, 95% CI 1.20-2.30), however, the studies on which this observations had been based were conducted prior to the recent increase in fluoroquinolone resistance.

Tigecycline, a tetracycline derivate and the first glycylcycline, received a black box warning and the FDA recommends against its use unless no other better alternative agents are available. However, if the higher mortality was due to a lower efficacy of the drug, one would expect lower cure rates, which was not the case in the systematic review by Shen et al. 2015[155], who did not find a difference in clinical and microbiological cure as compared to imipemen or ceftriaxone plus metronidazole.

In summary, for most comparisons, the precision in the summary estimates is very wide, and none met our definition of non-inferiority, thus, a clinically significant difference cannot be ruled out. Furthermore, the review of the clinical trial evidence does not point to superior of single agents or combination regimens. When we found statistically significant differences, these were obtained by aggregating several antibiotics groups at the expense of capacity to identify discrete antibiotics

determining better effects. Since this overview of systematic reviews yielded indeterminate findings, recommendation for the EML are based on CPGs.

Synopsis of guidelines[157]

We reviewed 8 guidelines, with quality scores ranging from 65% to 83%.[157-164] Some of the guidelines retrieved that we did not consider were for a local community[161], specific syndromes (appendicitis[162] or diverticulitis[157], which are not considered complicated intra-abdominal infections), a summary of other published guidelines or review articles[163, 164], or a recommendation on choice of a particular antibiotic.[160] Eventually, two guidelines were considered relevant for this review[158, 159].

The highest rated guideline, from IDSA[158], summarized recommendations for empiric therapy. A very comprehensive approach in terms of antibiotic choices had been used in this CPG, ending to recommend a large list of antibiotics which includes several overlapping agents. This approach differs from the parsimony spin of the essential medicines list.

Children

For community acquired infection in children, the recommendations are aminoglycoside-based regimens (gentamicin or tobramycin in combination with metronidazole or clindamycin with or without ampicillin), a carbapenem (ertapenem, meropenem, imipenem), a beta-lactam/beta-lactamase inhibitor combination (piperacillin-tazobactam, ticarcillin-clavulanate), or advanced-generation cephalosporins (cefotaxime, ceftriaxone, ceftazidime, cefepime) plus metronidazole. With severe beta-lactam allergies, either an aminoglycoside or ciprofloxacine plus metronidazole are recommended.

Adults

Single agent empiric therapy for adults with mild to moderate severity included cefoxitin, ertapenem, moxifloxacin, tigecycline, and ticarcillin-clavulanic acid. For high risk or severely ill adults, imipenem, meropenem, doripenem, and piperacillin-tazobactam were recommended. Recommended combination regimens include a cephalosporin (cefazolin, cefuroxime, ceftriaxone, cefotaxime, ciprofloxacin or levofloxacin), each in combination with metronidazole for mild to

moderately severe infections. For high risk community-acquired cases or severely ill patients, a carbapenem, piperacillin-tazobactam, a fluoroquinolone (ciprofloaxacin or levofloxacin) or a cephalosporin (cefepime, ceftazidime) each in combination with metronidazole are recommended. The guidelines also make recommendations for empiric therapy for health care-associated complicated intra-abdominal infections. If ESBL- producing Enterobacteriaceae are seen locally, then regimens including a carbapenem and aminoglycsides, but not cephalosporins are recommended. Ceftazidime is not recommended where > 20% *P. aeruginosa* are resistant. Vancomycin is recommended in addition to other antibiotics when coverage for MRSA is needed based on the local antibiogram. For the empiric therapy of acute cholecystitis, cefazolin, cefuroxime, or ceftriaxone is recommended for mild to moderately severe community acquired infection. A carbapenem (imipenem, meropenem, doripenem), piperacillin-tazobactam, a fluoroquinolone (levofloxacin or ciprofloxacin), or cefepime, each in combination with metronidazole is recommended for severe community acquired cholecystitis. For acute cholangitis following bilio-enteric anastomosis, or for healthcare associated biliary infection of any severity, any of the aforementioned antibiotics in combination with metronidazole could be used. The guidelines recommend against the use of ampicillin-sulbactam due to high resistance rates amongst *E. coli*, and against the use of cefotetan and clindamycin because of resistance in the Bacteroides fragilis group, aminoglycosides in non-severe, non-hospital-acquired cases, and recommends caution when using fluoroquinolones because of increasing resistance rates.

In contrast to the IDSA guidelines, the World Society of Emergency Surgery (WSES) guidelines[159] recommend either amoxicillin-clavulanate or ciprofloaxin and metronidazole for extra-biliary or biliary acute intra-abdominal infection in patients that are not critically ill who have no risk factors for ESBL. In those at increased risk for ESBLs and not critically ill, these guidelines recommend ertapenem or tigecyline for extra-biliary disease and tigecyline for intra-biliary disease. In critically ill patients with no risk for ESBLs, the guidelines recommend pipercillin-tazobactam for either extra and intrabiliary disease. Where there is an increased risk of ESBL, meropenem or imipenem with the option of adding fluconazole for extrabiliary disease and piperacillin and tigecyline for intra-biliary disease with the option of fluconazole are listed. For hospital acquired intrabdominal infection in the absence of critical illness where there is a risk for a multi-drug resistant organism, the guidelines recommend piperacillin, tigecycline, and fluconazole. For hospital acquired infection in a critically ill patient, piperacillin, tigecycline, an echinocandin (caspofungin or anidulofungin, or micofungin) or a carbapenem (meropenem, imipenem, doripenem), teicoplanin, and an echinocandin (caspofungin or anidulofungin, or micofungin) are recommended.

Antibiotic selected as essential:

The listing of antibiotics was based on the setting (community versus hospital-acquired), as well as based on severity applying the same approach as used in the IDSA guidelines.

For community-acquired non-severe infections, amoxicillin/clavulanate PO/IV or a cephalosporin (cefotaxime and ceftriaxone) with metronidazole fulfil the curative as well as the resistance preservative intent. For hospital-acquired or severe cases, the same cephalosporins with metronizole can be used, or piperacillin/tazobactam instead of amoxicillin/clavulanate.

Fluoroquinolones should be considered second line for patients who have contraindications to betalactams/cephalosporins due to resistance concerns, and concerns about potential harm (FDA boxed warning). Of the fluoroquinolones, moxifloxacin has not been added to the list despite recommendations in one guideline due to the availability of many other options and given the signal for higher adverse event rates. Vancomycin should be used for patients with concerns about a MRSA infection. We did not list teicoplanin due to redundancy and several indications for vancomycin across all syndromes. Ceftazidime, meropenem, and the aminoglycosides are listed as targeted antibiotics based on local resistance data as alternative options to the core antibiotics. Ampicillin can be considered if additional enterococcal coverage is needed if the used regimen would otherwise not be covering entorococcus (e.g. ceftriaxone/metronidazole).

Of the antibiotics listed in the guidelines, we did exclude cefazolin, cefoxitin and cefuroxime for redundancy, as ceftriaxone is listed which also offers broader gram-negative coverage. We also excluded ticarcillin-clavulanate and piperacillin as piperacillin-tazobactam is considered more appropriate and is listed for several syndromes. Tigecyclin has a potential role as a niche or last resort antibiotic for multi-resistant pathogens or if all first- and second line antibiotics cannot be used, but was not considered as a core or targeted antibiotic due to the black box warning by the FDA related to the presumed higher mortality rate. Cefepime was not added as it was felt to be redundant with the antibiotics already listed above, and the potential concern about inferiority in terms of mortality (see chapter in immunocompromised hosts). We also did not list ampicillin-sulbactam, cefotetan, and clindamycin as their use is discouraged in the IDSA guideline due to resistance concerns.

Ertapenem was added to the reserved list as it is considered a niche antibiotic, in particular for patients with suspected ESBL when *P. aeruginosa* coverage is not needed. We are only listing meropenem of the other available carbapenems as it is the most frequently recommended carbapenem across all syndromes, and we therefore excluded imipenem and doripenem.

Community-acquired cIAI, not severe:

Antibiotic	Adults (per dose)	Paediatrics (per day)	SR	CPG	EML (P/A)	List
Amoxicillin/clavulanate	1g/62.5mg PO			√	+/+	c
Cefotaxime	1-2g IV	150-200mg/kg IV		√	(+)/(+)	c
Or ceftriaxone	1-2g IV	50-75mg/kg IV		√	+/+	c
Metronidazole	500mg IV/PO	30-40mg/kg IV		√	+/+	c
Levofloxacin	750mg PO/IV			√	-/-	t
Or ciprofloxacin	500mg PO/400mg IV	20-30mg/kg IV		√	+/+	t

Severe community-acquired cIAI and all hospital-acquired cIAI:

Antibiotic	Adults (per dose)	Paediatrics (per day)	SR	CPG	EML (A/P)	List
Ampicillin	2g IV	200mg/kg IV		√	+/+	t
Piperacillin-tazobactam	3.375g IV	200-300mg/kg IV		√	-/-	c
Cefotaxime	1-2g IV	150-200mg/kg IV		√	(+)/(+)	c
Or ceftriaxone	1-2g IV	50-75mg/kg IV		√	+/+	c
Levofloxacin	750mg PO/IV			√	-/-	t
Or ciprofloxacin	500mg PO/400mg IV	20-30mg/kg IV		√	+/+	t
Ceftazidime	2g IV	150mg/kg IV		√	(+)/(+)	t

Meropenem	1g IV	60mg/kg IV	√	-/-	t
Gentamicin	5-7mg/kg IV	3-7.5mg/kg IV	√	+/+	t
Or Tobramycin	5-7mg/kg IV	3-7.5mg/kg IV	√	-/-	t
Metronidazole	500mg IV/PO	30-40mg/kg IV	√	+/+	c
Vancomycin	15-20mg/kg IV	40mg/kg IV	√	(+)/(+)	t

The recommended maximum duration of treatment is 4-7 days, unless source control had not been achieved and/or the patient is not improving clinically. Bowel injuries that are repaired within 12 hours and any other intra-operative contamination does not need treatment beyond 24 hours.

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