



Newsletter

Vol. 36 - Number 2 - October 2023

CONTENTS

Feedback from ISDB Committee meetings.....	1
NoGracias Platform: Your Web Page at ISDB.....	2-3
A graphic tool to promote the appropriate use of antibiotics in the community setting in the Local Health Authority of Verona - Italy.....	3
Lower urinary tract infection.....	4
Pharyngitis.....	5
Acute sinusitis.....	6
Bronchitis.....	7
Acute otitis media.....	8
Additional references on the appropriate use of antibiotics and the fight against antimicrobial resistance.....	9
New drug submissions in Canada and a comparison with the Food and Drug Administration and the European Medicines Agency: Cross-sectional analysis.....	10

WELCOME TO THE SECOND ISDB NEWSLETTER OF 2023

In this issue you will find a short up-date on ongoing work of the ISDB Committee. NoGracias platform, the ISDB associate member from Spain, provided a contribution on its mission and activities.

Most of the newsletter is dedicated to the appropriate use of antibiotics. An initiative that uses infographics to illustrate key messages on appropriate antibiotic use for common conditions has been made available by InfoFarma, the Italian ISDB member. A list of recent publications on antimicrobial resistance provides further information.

Last but not least, you will find an abstract of an article from Joel Lexchin on new drug submissions in Canada and a comparison with the US FDA and the EMA.

The next Newsletter is planned for Spring 2024. We welcome comments, suggestions and articles. Please send them to: rkessler@prescrire.org by end of January 2024.

Feedback from ISDB Committee meetings

Since April 2023, the Committee held three online meetings. The Committee is happy to announce that *Australian Prescriber* has a new publisher, Australia's Therapeutic Guidelines, which was previously an ISDB member. As *Australian Prescriber* is able to maintain editorial independence and fulfil ISDB membership criteria, it will remain a full ISDB member organisation. We welcome *Australian Prescriber* back to ISDB.

The two working groups devoted to the ISDB Strategic Plan (one focusing on the ISDB membership and the other on ISDB mission and activities) continued their discussions during summer. A survey of ISDB members will be launched soon to identify members' needs, views and availabilities to actively engage in ISDB activities.

NOGRACIAS PLATFORM: YOUR WEB PAGE AT ISDB

By Roberto Sánchez, president of NoGracias



Nowadays, webpages or content blogs have less relevance on the Internet. We could list three reasons, although there are probably more. Firstly, it may be that the theoretical framework for a specific content area has become saturated and there is little more to say. Secondly, Social Networks lead us to be brief, superficial and to express feelings rather than to explore issues in depth, taking our time and focusing on quality. Thirdly, the lack of incentives results on poor consistency and it is a frequent annihilator.

From that perspective, the contents of a hypothetical web page in the subsector of Health Sciences, using critical approach, would have everything against it. Even more so, if the focus or object of study involves the pharmaceutical industry and the pharmaceutical field. That is why the survival of a web page like NoGracias Platform, with more than 10 years of history, is a real miracle. Almost all web pages in this area are privately financed (by pharmaceutical industry) or belong to the public sector (institutions, foundations, ministries). The NoGracias page does not receive any kind of funding and all contributors and administrators are uncompensated volunteers.

The Platform NoGracias is a legal and registered organisation which defends a public health care system in a context of democratic governance with all its attributes (transparency, accountability and responsibilities). It promotes and defends the good governance of health institutions and scientific and professional ethics. It seeks to limit or denounce inappropriate influence, focusing on industries that condition professional practice (pharmaceuticals, but also the food and technology industries). It was created at the same time that emerged the international “No Free Lunch” movement (which was meant to indicate: “we don’t want the industry to invite us to eat, thank you”). In this sense, it also embraces scientific research and other activities that result in undue influence, such as: the money that industries

give to healthcare professionals; questionable decision-making processes in public administrations and in the development of public policies; the manipulation of the media, public opinion, industry stakeholders or patients’ interests.

The webpage reflects the characteristics of the organization. It is a web page with predominantly general health content, allowing us to reflect a broad and deep perspective. Some areas of interest stand out such as psychiatry, philosophy of science, bioethics and public health in line with the interests of the most prolific contributors. The industry’s agenda also affects our content, for example, during the last decade we wrote about cardiovascular risk factors and their pharmacological remedies, now we publish more on issues related to immunology. Our target population has always been the general public but due to our professional “deformation” we do not always use language appropriate for the general public, we kind of stay in the middle ground between aiming at the public and at health professionals.

From the beginning we understood that it was necessary to do a third or fourth review of the scientific evidence. We decided we would start by using the studies and the primary data (although Erviti and his team have recently shown that there could be discrepancies between the two and that the studies may not accurately reflect the underlying data). Subsequently, we search for aggregated analysis (systematic reviews and meta-analysis). Thirdly, we would request the evaluations of pharmacists, gathering their different perspectives, which, so far, are the most trusted secondary data sources; we use their position papers, evaluation reports or pharmacotherapeutic bulletins. Moreover, they provide meaningful information because they know the geographical context in which we work, not only patients but also our regulatory standards. Taking into account our local environment is also useful to evaluate the prescribing behaviour in the different geographical areas through the use of indicators. We know that we have had an influence while following the process we have described, but the success of the NoGracias Platform and its analyses is primarily due to what we are about to describe.

The evidence and recommendations emanating from the process described above are not transferred to clinical practice like someone pouring water into a glass; they must follow a journey that we might call “the social system of influence”: a social network in which meanings and practices are expressed and there is a correlation of force between different actors, where hierarchies and, above all, power re-

lations weigh heavily. Let's say that one of our comparative advantages in relation to other organisations is that we specialise in studying the interests and behaviours of different influencers or industry stakeholders (Scientific Societies, Key Opinion Leaders or Experts, Patient Associations, the media, healthcare professionals, patients or the general public). We try to understand why they do what they do, and how and when they do it. In this sense, and in relation to the scientific aim of our work, we can anticipate and explain to our readers the characteristics, mechanisms and instruments used to exert influence.

We think that the sharp and often quantitative analysis of the evidence is just as necessary as the other steps described above. Of course, influence works in an interactive relational system: it collects information and uses it later. For this reason, we think that the contributions that organizations such as NoGracias in Spain and counterparts in other countries can make to the great work that the ISDB does are important.

<https://www.nogracias.org/>

A graphic tool to promote the appropriate use of antibiotics in the community setting of the Local Health Authority of Verona - Italy

Authors: F. Schmid¹, L. Dal Mas¹, A. Ossato¹, R. Joppi²

Affiliation: ¹School of Specialization in Hospital Pharmacy - University of Padua; ²Pharmaceutical Department of the Local health Authority of Verona

The appropriate use of antibiotics, defined as using the correct drug, in the optimal dosage and for the correct duration, is associated with fewer side effects and reduced likelihood of antimicrobial resistance (AMR) [1,2]. Antimicrobials are drugs used to prevent and treat infections in humans, animals and plants, killing or inhibiting the growth of microorganisms, such as bacteria, viruses, fungi and parasites. They include antibiotics, antivirals, antifungals and antiparasitics [3].

Microorganisms can be intrinsically resistant to some antimicrobials, but they can also acquire resistance through exposure to antimicrobials. AMR occurs when microorganisms resist antimicrobials able to kill them or prevent their growth and leads to a lack of efficacy of antibiotics and other antimicrobial medicines. It makes infections harder to treat, increasing the risk of severe illness, and is estimated to contribute to more than five million deaths each year worldwide [4].

On 9th December 2022, the World Health Organization (WHO) published the WHO AWaRe (*Access, Watch, Reserve*) antibiotic book, a manual for the appropriate use of antibiotics which provides clear and immediate information on the choice of antibiotic, dose and duration of therapy, through the use of infographics [4].

In order to promote appropriate use of antibiotics, we integrated information from the WHO antibiotic manual and the Local Health Authority of Verona - Veneto Region.

We extracted infographics from the WHO AWaRe antibiotic book on the most frequent infections in the community setting: lower urinary tract infection, pharyngitis, acute sinusitis, bronchitis and acute otitis media. A multidisciplinary team (infectious disease specialists, hospital pharmacists and general practitioners) adapted the information to the local setting and drafted the infographics using a graphic design tool, with the aim to disseminate these infographics for use in clinical practice.

Readapted infographics for each infection, with indication of symptomatic and antibiotic treatments, are presented on the following pages.

References

1. Dylis, A., Boureau, A., et al.: Antibiotics prescription and guidelines adherence in elderly: impact of the comorbidities. *BMC Geriatr.* 19, 291 (2019).
2. Piano Nazionale di Contrasto all'Antibiotico-Resistenza (PNCAR) 2022-2025.
3. <https://www.consilium.europa.eu/en/press/press-releases/2023/06/13/tackling-antimicrobial-resistance-council-adopts-recommendation/pdf>
4. <https://www.who.int/publications/i/item/9789240062382>



LOWER URINARY TRACT INFECTION

Treatment considerations

Antibiotic treatment recommended if compatible clinical presentation (signs and symptoms) AND a positive test (positive urine leucocytes/leucocyte esterase or positive urine culture).

ASYMPTOMATIC BACTERIURIES SHOULD NOT BE TREATED AND, IF PRESENT, VESICAL CATHETER SHOULD BE REPLACED BEFORE URINE CULTURE. IN THE ABSENCE OF SYMPTOMS DO NOT CARRY OUT URINE CULTURE.



Antibiotic Treatment

Empiric antibiotic therapy in the absence of signs and symptoms of systemic infection:



Uncomplicated

Nitrofurantoin 100 mg oral q6h (only in the female sex)

 Antibiotic treatment duration: 5 days

Nitrofurantoin is the preferred treatment option for acute lower UTI and is active against most ESBL-producing isolates

or

Fosfomycin trometamol 3 g oral

 Antibiotic treatment duration: single dose



At risk of complication*

Fosfomycin trometamol 3 g oral

 Antibiotic treatment duration: single dose

or

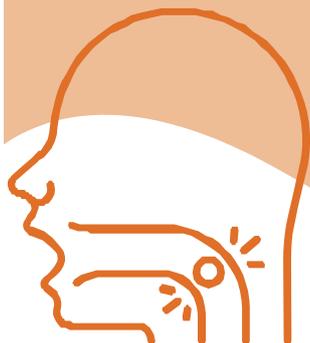
Amoxicillin+clavulanic acid 1 g oral/1.2 g IV q12h

 Antibiotic treatment duration: 7 days

If UTI history from MDR germs in the previous 12 months:

- Preferably wait for the antibiogram.
- If necessary start empirical therapy: fosfomycin trometamol 3 g q48h (continue with 3 total doses if sensitive)

**Presence of one or more risk factors: presence of urinary catheter, ureteral stent, urinary diversion; obstructive uropathy (benign prostatic hypertrophy, neurogenic bladder, calculosis, neoplasms); vesicoureteral reflux or other functional abnormalities; positive history of radiotherapy or surgical procedure in the urinary tract; chronic kidney disease; transplant; diabetes mellitus; immunodepression.*



PHARYNGITIS

Treatment considerations

Antibiotic treatment is not necessary in most cases (often viral etiology).

Consider starting antibiotic therapy based on **Fever-PAIN score***:

Score 0-1: 13 to 18% likelihood of isolating streptococcus: antibiotic treatment is **NOT** indicated.

Score 2-3: 34 to 40% likelihood of isolating streptococcus: prescription and start therapy at 3-5 days if no improvement.

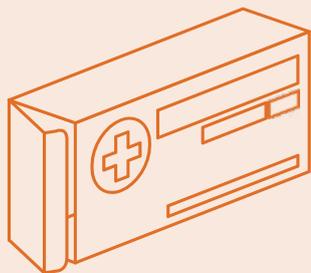
Score >4: 62 to 65% likelihood of isolating streptococcus: immediate start of therapy or indication to start at 48 hours if no improvement in the milder cases.

***Fever-PAIN score:**

- Fever (> 38°C, during previous 24 hours) - 1 point.
- Purulence (pus on tonsils) - 1 point.
- Attend rapidly (within 3 days after onset of symptoms) - 1 point.
- Severely inflamed tonsils - 1 point.
- No cough or coryza (inflammation of mucus membranes in the nose) - 1 point.



Symptomatic Treatment



Ibuprofen

400 mg 2-4 times a day;
 600 mg 1-3 times a day;
 Max: 1800 mg/day

or

Paracetamol (acetaminophen)

500 mg-1000 mg at intervals not less than 4 hours;
 Max: 3000 mg/day

If Fever-PAIN score ≥ 2 Antibiotic Treatment



First Choice:

Amoxicillin+clavulanic acid oral

Dosage and duration of treatment:
 1 g q12h for 5-10 days



Second Choice:

Clarithromycin oral

Dosage and duration of treatment:
 500 mg q12h for 5-10 days

Azithromycin oral

Dosage and duration of treatment:
 500 mg q24h for 5-10 days

Clindamycin oral

Dosage and duration of treatment:
 300 mg q8h for 5-10 days

All dosages are for normal renal function

ACUTE SINUSITIS



Treatment considerations

- The aim of treatment is to improve symptoms, but antibiotics have minimal impact on symptom duration in most cases
- Symptomatic treatment includes antipyretic and analgesic medications, nasal irrigation with a saline solution and topical intranasal glucocorticoids or decongestants
- Most guidelines recommend basing treatment decisions on disease severity (duration and intensity of symptoms)



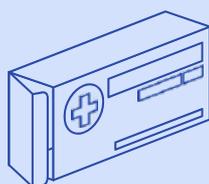
Antibiotic treatment is not needed in most cases (often viral etiology).

- In case of symptoms <10 days **antibiotic treatment is not indicated**
- In case of symptoms >10 days consider prescription with delayed start based on the likelihood of bacterial infection, starting therapy if rapid worsening or no improvement at 7 days

Antibiotics should be considered if:

- Severe onset of symptoms (fever ≥ 39.0 °C and purulent nasal discharge or facial pain for at least 3–4 consecutive days)
- Patients at increased risk of complications e.g. those with chronic underlying comorbid diseases
- Alarm signs/symptoms suggestive of complicated infection such as systemic toxicity, persistent fever ≥ 39.0 °C, periorbital redness and swelling, severe headache, or altered mental status

Symptomatic Treatment



Ibuprofen

400 mg 2–4 times a day;
600 mg 1–3 times a day;
Max: 1800 mg/day

or

Paracetamol (acetaminophen)

500 mg–1000 mg at intervals not less than 4 hours;
Max: 3000 mg/day

Antibiotic Treatment

 **First Choice:**

Amoxicillin+clavulanic acid 875 mg + 125 mg oral q8h

 **Treatment duration:** 5 days

+

inhaled steroid for 14 days

 **Second Choice:**

Clarithromycin 500 mg oral q12h

 **Treatment duration:** 5 days

+

inhaled steroid for 14 days

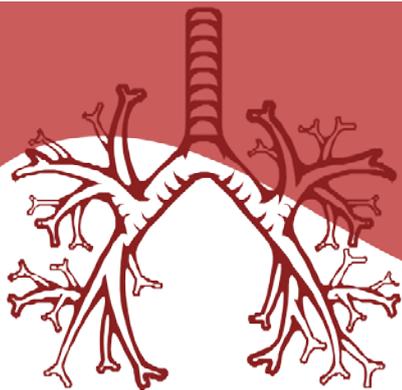
or

Doxycycline 100 mg oral q12h

 **Treatment duration:** 5 days

All dosages are for normal renal function

Medicines are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated



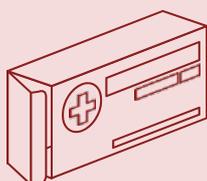
BRONCHITIS

Treatment considerations

Antibiotic treatment is not needed in most cases (most are of viral origin).
 Antibiotic treatment may be useful in patients with COPD.



Symptomatic Treatment



Ibuprofen

400 mg 2-4 times a day;
 600 mg 1-3 times a day;
 Max: 1800 mg/day

or

Paracetamol (acetaminophen)

500 mg-1000 mg at intervals not less than 4 hours;
 Max: 3000 mg/day

Antibiotic Treatment

Antibiotics should be considered if:
 age > 80 years + 1 criterion or
 age > 65 years + 2 criteria.

Criteria:

- Hospitalization in the last year;
- Therapy with oral steroids;
- Insulin-dependent diabetes;
- Heart failure;
- Severe neurological pathology/stroke.



Antibiotic Treatment:

Amoxicillin+clavulanic acid 875 mg + 125 mg oral q8h



Antibiotic treatment duration: 5 days

or



Clarithromycin 500 mg oral q12h



Antibiotic treatment duration: 5 days

or



Doxycycline 100 mg oral q12h

Antibiotic treatment duration: 5 days

All dosages are for normal renal function

Medicines are listed in alphabetical order and should be considered equal treatment options



ACUTE OTITIS MEDIA

Treatment considerations

- Most non-severe cases can be managed symptomatically with no antibiotic treatment
- Instruct patients to monitor symptoms and report back in case they worsen/persist after few days

Antibiotics should be considered in case of severe symptoms (e.g. systemically very unwell, ear pain despite analgesics, fever $\geq 39.0^{\circ}\text{C}$)



Symptomatic Treatment



Ibuprofen

400 mg 2-4 times a day;
 600 mg 1-3 times a day;
 Max: 1800 mg/day

or

Paracetamol (acetaminophen)

500 mg-1000 mg at intervals not less than 4 hours;
 Max: 3000 mg/day

Antibiotic Treatment

Consider prescription with delayed start in case of no improvement at 48-72 h or immediately for analgic purpose.



First Choice:

Amoxicillin+clavulanic acid 875 mg + 125 mg oral q12h



Treatment duration: 5 days



Second Choice:

Clarithromycin 500 mg oral q12h



Treatment duration: 5 days

or

Levofloxacin 750 mg oral q24h



Treatment duration: 5 days

All dosages are for normal renal function

Medicines are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated

Additional references on the appropriate use of antibiotics and the fight against antimicrobial resistance

WHO launches global network to detect and prevent infectious disease threats, 15 May 2023, <https://www.who.int/news/item/20-05-2023-who-launches-global-network-to--detect-and-prevent-infectious-disease-threats>

WHO outlines 40 research priorities on antimicrobial resistance, 22 June 2023
<https://www.who.int/news/item/22-06-2023-who-outlines-40-research-priorities-on-antimicrobial-resistance>

Supply-chain factors and antimicrobial stewardship
Kamere N, Rutter V, Munkombwe D et al.
Bull World Health Organ. 2023;101(6):403-411. doi: 10.2471/BLT.22.288650.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10225941/>

Global antimicrobial-resistance drivers: an ecological country-level study at the human-animal interface
Allel K, Day L, Hamilton A, Lin L, Furuya-Kanamori L, Moore CE, Van Boeckel T, Laxminarayan R, Yakob L.
Lancet Planet Health. 2023 Apr;7(4):e291-e303. doi: 10.1016/S2542-5196(23)00026-8.
[https://www.thelancet.com/journals/lanplh/article/PIIS2542-5196\(23\)00026-8/fulltext](https://www.thelancet.com/journals/lanplh/article/PIIS2542-5196(23)00026-8/fulltext)

Nephrotoxicity of Amoxicillin and Third-Generation Cephalosporins: An Updated Review
Garnier AS, Drablier G, Briet M. et al.
Drug Saf 46, 715-724 (2023). <https://doi.org/10.1007/s40264-023-01316-1>
<https://link.springer.com/article/10.1007/s40264-023-01316-1#citeas>

Antibiotic Resistance: Federal Agencies Have Taken Steps to Combat the Threat, but Additional Actions Needed
GAO-23-106776, April 27, 2023
<https://www.gao.gov/products/gao-23-106776>

Prudent use of antibiotics and more research needed to fight antimicrobial resistance
European Parliament, press release, 1st June 2023
<https://www.europarl.europa.eu/news/en/press-room/20230524IPR91916/prudent-use-of-antibiotics-and-more-research-needed-to-fight-amr>

The European Health Council (EPSCO) adopts a recommendation on stepping up EU actions to combat antimicrobial resistance, 13 June 2023
<https://www.consilium.europa.eu/en/meetings/epsco/2023/06/12-13/>

Statement by ReAct - in response to the EC's proposal for revising EU pharmaceutical legislation, 26 April 2023
<https://www.reactgroup.org/news-and-views/news-and-opinions/2023-2/statement-by-react-in-response-to-the-ecs-proposal-for-revising-eu-pharmaceutical-legislation/>

HAI: [The Antimicrobial Resistance Toolkit](#)

New drug submissions in Canada and a comparison with the Food and Drug Administration and the European Medicines Agency: Cross-sectional analysis

Lexchin J

PLoS ONE 2023; 18(6): e0286802. <https://doi.org/10.1371/journal.pone.0286802>

Abstract

➔ Background

Health Canada posts the outcomes of all New Drug Submissions. In some cases, companies have withdrawn submissions or submissions have been rejected by Health Canada for new active substances (NAS). This study explores the reasons for those decisions and compares them with decisions made by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

➔ Methods

This is a cross-sectional analysis. Submissions for NAS between December 2015 and December 2022 were identified along with the original indications for the NAS, the information that Health Canada had available and the reasons for its decisions. Similar information was sourced from the FDA and the EMA. Their decisions were compared to those made by Health Canada. The time between decisions by Health Canada, the FDA and the EMA were calculated in months.

➔ Results

Health Canada considered 272 NAS and approved 257. Sponsors withdrew 14 submissions for 13 NAS and Health Canada rejected submissions for 2 NAS. The FDA approved 7 of these NAS and the EMA approved 6, rejected 2 and submissions were withdrawn by 2 companies. Health Canada and the FDA considered similar information in 4 of 7 cases. Indications were the same except in one case. The FDA made decisions a mean of 15.5 months (interquartile range 11.4, 68.2) before companies withdrew their submissions from Health Canada. There were 5 cases where Health Canada and the EMA considered the same information and in 2 of those the outcome was different. Health Canada and EMA decisions were generally made within 1-2 months of each other. Indications were the same in all cases.

➔ Conclusions

Differences in decision making by regulators are due to more than the data which with they are presented, the timing of the presentations and the indications for the drugs. Regulatory culture may have influenced decision making.