Clinical Pharmacology & Toxicology Pearl of the Week

~ Causality Assessment Tools, Part 1: Naranjo Scale ~

Case:

A 70-year-old female develops a morbilliform rash approximately 10 days after receiving antibiotics for septic arthritis. She received vancomycin and piperacillin/tazobactam initially, which was changed to cefazolin after cultures showed MSSA. She is currently on the cefazolin. There is no evidence of new onset end organ damage, but the eosinophil count is slowly increasing.

You are consulted by the bedside team for an opinion on which of her medications could have caused this rash as she is supposed to receive a total of 4 weeks of antibiotics for her septic arthritis treatment. Decisions need to be made about continuing versus stopping the antibiotics.

What tool(s) will you use to help determine drug causality?

Background:

- ✓ An adverse drug reaction (ADR) is defined as a noxious and unintended response to a drug administered at doses normally used for desired effect.
- ✓ There are consequences for ADRs as they produce significant morbidity and mortality.
- ✓ In Canada, more than 1 in 9 Emergency Department visits are due to drug-related adverse events, and medication and fluid-related events are the second-leading cause of hospital-based adverse events behind surgical complications.

Causality Assessment Tools:

- ✓ Prior to the development of tools, decisions on stopping or continuing medications were often left to clinical judgement/expert opinion.
- ✓ These decisions are important for patients who may be at risk of worsening disease by avoiding the drug.
- ✓ Causality analysis (CA) is an approach that helps to determine a causal link between medication and patient harm (i.e. an ADR).
- ✓ While numerous CA tools exist, there is no gold standard.
- ✓ There are several causality assessment tools that have been developed. These include the Naranjo Scale, the Liverpool Causality Assessment Tool, and the WHO-UMC causality assessment. There are also specific tools for specific conditions, like RUCAM for liver injury, and J-SCAR and REGISCAR for DRESS Syndrome.
- ✓ Difficulties in establishing causality assessments with decisional algorithms are often due to the presence of confounding variables.
- ✓ Confounding variables include underlying disease, concomitant use of other drugs, absence of published data, and effect of dechallenge or rechallenge of simultaneous drugs (if performed). This affects both intra and inter-rater reliability.
- ✓ An individual's clinical expertise remains essential to appropriate causality analysis.
- ✓ It is often recommended to use more than one tool in practice when performing an assessment. As such, it is important to know the strengths and limitations of several tools.

Naranjo Scale:

- ✓ Comprised of 10 questions with each response assigned a score. Total score corresponds to likelihood of drug-related ADR. Score ≥ 9 = definite; 5–8 = probable; 1–4 = possible; ≤ 0 = doubtful.
- ✓ Limitations include the effect of confounders as 'alternative causes', the absence of blood/other fluid levels of drugs in many cases, the fact that rechallenge with a culprit drug may not be safe or appropriate, and that giving a placebo is usually limited to clinical trials and experimental studies.

Table I. *ADR probability scale*

To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score.

	Yes	*No*	*Do not know*	*Score*
1. Are there previous *conclusive* reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	−1	0	
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was readministered?	+2	−1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0	
6. Did the reaction reappear when a placebo was given?	−1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
			Total score	

References:

1. Um et al. Comparison of the Liverpool Causality Assessment Tool vs. the Naranjo Scale for predicting the likelihood of an adverse drug reaction: A retrospective cohort study. BJCP 2023;1-6.
2. Baker et al. The Canadian Adverse Events Study. CMAJ 2004;170(11):1678-86.
3. Deutscher et al. A scoping review of the clinical utility of adverse drug reaction causality analysis tools for use in the hospital setting. Exp Rev Clin Pharm 2024.
4. Naranjo et al. A method for estimating the probability of adverse drug reactions. Clin Pharm Ther 1981.

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm, excluding stat holidays. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral, Specialist Link, and RAAPID. You can also find us in the Alberta Referral Directory (ARD) by searching "Pharmacology" from the ARD home page. Click HERE for more details about the service.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

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