Going Nsane over NSAIDS:
Evaluation of the evidence behind the rejection of ibuprofen in management of COVID-19

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Disclosures

- I have no conflicts of interest to declare

Learning Objectives

- Review what has been said about using ibuprofen/NSAIDs in patients with suspected/confirmed COVID-19 infection in the media and literature

- Evaluate the evidence behind these statements, if any

- Understand how to properly apply concepts of prior and biologic probabilities when maintaining healthy skepticism in a quickly-evolving setting

- Consider the physiological likelihood of the claims being made

- Develop a strategy for communicating this information to other HCPs and to the public

How did we get here?

- Step 1: on March 11th the BMJ publishes an article titled "Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?", based on an n=191 retrospective cohort study on the clinical course and risk factors for mortality published in The Lancet the same day
  - In the BMJ article, the authors needlessly try to explain these comorbidities by linking them to the use of ACEi/ARB medications
    - A great alternative explanation would be that these are common comorbidities for many illnesses because these patients tend to be sicker in general
  - They theorize that because ACE2 is used by coronaviruses to bind to target cells in humans, that upregulation of these receptors in ACEi/ARB users (along with ibuprofen/NSAIDs and glitazones) causes the increased risk of serious infection in these patients

How did we get here?

- Step 2: French health minister Oliver Veran tweets on March 14th that anti-inflammatory drugs like ibuprofen and cortisone could aggravate the infection, and paracetamol (acetaminophen) should be used for fever

  - This was apparently based on an n=4 unpublished case series he heard about from an ID doc in southern France who had patients develop serious symptoms who had also used NSAIDs

  - A bunch of European doctors/professors jumped into the media to support the claim, claiming (but not actually citing) various studies on NSAIDs worsening respiratory disease, and effects on ACE2

How did we get here?

- Step 3: On March 17th, the WHO put out a statement that they also recommended against the use of ibuprofen for treating fevers related to COVID-19
  - They would retract this statement the next day
- Step 4: This evidence-adjacent (and often evidence-free) back and forth led to a confusing media frenzy that has left not only patients but also many health care professionals with no idea what to do
  - Anecdotally, I've even heard calls to remove ibuprofen from formularies/stock lists temporarily to avoid accidental use!

Is there anything to these statements?

- ACE2 receptor upregulation allowing for increase coronavirus binding is purely a theoretical interaction at this point with no meaningful clinical data to support the claim

  - Hypertension Canada on March 13th: *".... there is no evidence that patients with hypertension or those treated with ARB or ACE inhibitor antihypertensive therapy are at higher risk of adverse outcomes from COVID19 infection"*

  - ACC/AHA/HFSA Statement on March 17th: *".... there are no experimental or clinical data demonstrating beneficial or adverse outcomes among COVID-19 patients using ACE-I or ARB medications"*

Is there anything to these statements?

- Anti-inflammatory effect stunting immune response also makes physiologic sense, and we even have some data here in CAP
  - 2010 prospective cohort study in CHEST of n=90 ICU/Step-down patients in France
    - 32 ambulatory NSAID users and 58 non-users
    - NSAID group was a little younger, less sick at admission (but had symptoms for longer), stayed in hospital a little longer, had more pre-hospital abx,
      - 53 total analyses done so some of these are almost certainly false positives from over-testing
  - 2016 prospective observational study in Respiratory Medicine of n=57 hopsitalized pneumonia patients in Greece
    - 36 users, 21 non-users
    - NSAID group had prolonged hospital stay and more pleural effusions needing drainage

Is there anything to these statements?

- 2016 prospective cohort study in Lung of n=221 non-immunocompromised hospitalized CAP patients at a university hospital in France
  - Only 24 NSAID users vs 197 non-users
  - NSAID users were younger and healthier, but had pre-hospital symptoms for longer and took longer to get proper abx. They had more pleuroparenchymal complications, but a similar length of stay
    - This study also did a huge number of tests (47), so over-testing a problem again
- 2019 review in the Journal of Clinical Medicine said that the association between NSAID use and CAP-complications is "strongly supported", but with an unknown mechanism
  - I would argue "strongly supported" is a little bit much for a series of small and weak observational trials that don't always agree with each other

Biologic Probability

- How "anti-inflammatory" are OTC/antipyretic doses of ibuprofen in reality?
  - Antipyretic doses are generally <1200 mg/day, whereas anti-inflammatory doses (such as those used in Rheumatoid Arthritis) are in the range of 2400-3200 mg/day
- Further, if these doses of ibuprofen had significant anti-inflammatory effects, would we not see this as a class-effect harm for any anti-inflammatory drugs?
  - Some people still argue in favour of glucocorticoids to treat severe pneumonia
  - There are also multiple anti-inflammatory biologic drugs being studied for the treatment of COVID-19 right now, including tocilizumab, IVIG, eculizumab, and leflunomide, amongst others
    - Some argue that an anti-inflammatory medicine must be a component of therapy to avoid cytokine storm

Prior Probability

- There is some weak data behind respiratory infections being affected, but all observational and without a conclusive cause-effect relationship
  - That review article could not comment on a mechanism
    - Supposed that intrinsic neutrophil recruitment may be the issue
    - Also postulated that symptom control could lead to a delayed presentation and delay in antibiotic administration
  - Could this also be a bradykinin effect confounding symptomatology?
- And if it was a true effect, would we not see this in other infections too?
  - NSAIDs are an effective treatment for uncomplicated UTI
  - From a viral perspective, NSAIDs are 1st line treatment for viral pericarditis

So what do we tell people?

- The ACE2 thing is quite unlikely and has zero data in humans to support it
- The Inflammatory response modulation has only been seen in community-acquired bacterial pneumonia and no other infections
  - Recall also that all this data is only in patients that eventually get sick enough to be hospitalized, we don't know what happens at a greater population level in the community
    - If we were to extrapolate this to (a) a viral infection that (b) the majority of cases are mild and able to be managed in the community (which to be clear, we should probably not do), you could also reasonably argue that the temporal explanation may be of benefit at keeping patients at home and out of hospitals/clinics for longer to help limit spread and lower strain on the healthcare system
      - Please note that I do not believe that, this is merely an exercise in pointing out the flaws in extrapolating such data and drawing such broad conclusions

So what do we tell people?

- Overall, a few one-off statements got way overblown
- Suggested effects on ACE2 are not based in human data
- Ambulatory use of NSAIDs might prolong length of stay, and they also delay time to presentation which may complicate course
  - However, this may actually be of benefit when we talk about flattening the curve, and we don't have enough outpatient data to see what this looks like in mild/moderate cases
  - All these statements are wild extrapolations that should be taken with a truck-load of salt
- Based on the best available evidence, Ibuprofen is a perfectly reasonable option for patients trying to control symptoms of COVID-19 infection

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Questions?
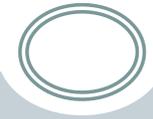
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