26 Appendix: Jarisch-Herxheimer Reaction

Jarisch-Herxheimer reaction (JHR) is an acute febrile reaction which may complicate the initiation of an effective treatment against infections due to intracellular micro-organisms[2221]. JHR can also be expressed as the worsening of symptoms or the appearance of new symptoms. JHR is traditionally associated with antibiotics and antivirals but may appear from anything that impacts the immune response or infections. If the action results in a pathogen being killed which releases chemicals that cause symptoms, a JHR may occur. For example, the use of NAC (Acetylcysteine) or EDTA has been reported to produce a worsening of symptoms or JHR. These two anti-biofilm compounds break down biofilms exposing pathogens to the immune system; they do not directing kill any pathogens.

Antibiotics increase the bioavailability of endotoxin from Gram-negative bacteria[2222]. The increase may be up to 20 fold more[2223]. It should be noted that the Gram-negative bacteria producing the endotoxins may be microflora.

A worsening of symptoms from something is helping is almost a trademark for CFS. Unfortunately, in many CFS communities there is concerns that any reaction may be *something* else happening; the conclusion of many patients is to "do no harm", thus avoiding JHR totally for fear (or not wishing to go through the misery of a JHR).

JHR can include:

- Acute rise in temperature, tachycardia, tachypnea, hypoxia, hypotension[2224]
- Associated with Gram-positive, Gram-negative or fungal organisms[2225]
- Associated with high titers[2226], high concentrations of TNF, IL-6, and IL-8[2227] [2228] up to 8 fold increase over pre-antibiotic levels[2229].
- Can last for hours and reoccur[2230]
- Caused by release of endotoxin-like material and cytokine elevation[2231] [2232] [2233].
- Delusional behavior, fever, rigors, tachycardia and hypoxia[2234] [2235] [2236], complex visual and auditory hallucinations[2237]

[2221] http://www.ncbi.nlm.nih.gov/pubmed/9733392 (1998)
[2222] http://www.ncbi.nlm.nih.gov/pubmed/7619330 (1995)
[2223] http://www.ncbi.nlm.nih.gov/pubmed/1445982 (1992)
[2224] http://www.ncbi.nlm.nih.gov/pubmed/19040755 (2008 *)
[2225] http://www.ncbi.nlm.nih.gov/pubmed/12122518 (2002)
[2226] http://www.ncbi.nlm.nih.gov/pubmed/20825309 (2010)
[2227] http://www.ncbi.nlm.nih.gov/pubmed/16455348 (2006)
[2228] http://www.ncbi.nlm.nih.gov/pubmed/9093599 (1997 *)
[2229] http://www.ncbi.nlm.nih.gov/pubmed/1569394 (1992)
[2230] http://www.ncbi.nlm.nih.gov/pubmed/19040755 (2008)
[2231] http://www.ncbi.nlm.nih.gov/pubmed/15896248 (2005)
[2232] http://www.ncbi.nlm.nih.gov/pubmed/9733392 (1998)
[2233] http://www.ncbi.nlm.nih.gov/pubmed/9511083 (1998)
[2234] http://www.ncbi.nlm.nih.gov/pubmed/22707695 (2012)

- Developed disseminated intravascular coagulation[2238].
- Feeling cold with worsening headache and chills[2239]
- Improves with antipyretic and anti-inflammatory agents[2240].
- Improves with dexamethasone treatment[2241]
- Improves with olanzapine treatment[2242].
- Improves with pre-treatment with anti-tumour necrosis factor antibodies[2243] [2244] [2245].
- Incidence varies by antibiotic and dosage[2246].
- Increase of IgG and IgM by 4x[2247]
- May show up as worst MRIs[2248] [2249]
- No standard for determining a JHR.
- Not uncommon to confuse drug allergy with JHR[2250].
- Pentoxifylline does not have any effect[2251].
- Potentially lethal[2252]
- Rates seen between 0.8%[2253] - 1.4%[2254] - 9%[2255] - 15%[2256] - 32%[2257] -34%[2258] - 40%[2259] - 43%[2260] [2261] - 47%[2262] - 54%[2263]
- Rise in body temperature (1 C)[2264]

[2235] http://www.ncbi.nlm.nih.gov/pubmed/20664452 (2010)
[2236] http://www.ncbi.nlm.nih.gov/pubmed/9610974 (1998)
[2237] http://www.ncbi.nlm.nih.gov/pubmed/12604286 (2002)
[2238] http://www.ncbi.nlm.nih.gov/pubmed/12182387 (2002)
[2239] http://www.ncbi.nlm.nih.gov/pubmed/16288069 (2005)
[2240] http://www.ncbi.nlm.nih.gov/pubmed/16288069 (2005)
[2241] http://www.ncbi.nlm.nih.gov/pubmed/18302644 (2008)
[2242] http://www.ncbi.nlm.nih.gov/pubmed/18635694 (2009)
[2243] http://www.ncbi.nlm.nih.gov/pubmed/15896248 (2005)
[2244] http://www.ncbi.nlm.nih.gov/pubmed/9093599 (1997 *)
[2245] http://www.ncbi.nlm.nih.gov/pubmed/8663853 (1998 *)
[2246] http://www.ncbi.nlm.nih.gov/pubmed/7784810 (1995)
[2247] http://www.ncbi.nlm.nih.gov/pubmed/8508816 (1993)
[2248] http://www.ncbi.nlm.nih.gov/pubmed/21042805 (2011)
[2249] http://www.ncbi.nlm.nih.gov/pubmed/18302644 (2008)
[2250] http://www.ncbi.nlm.nih.gov/pubmed/16288069 (2005)
[2251] http://www.ncbi.nlm.nih.gov/pubmed/8769625 (1996)
[2252] http://www.ncbi.nlm.nih.gov/pubmed/21803390 (2011)
[2253] http://www.ncbi.nlm.nih.gov/pubmed/19411042 (2009)
[2254] http://www.ncbi.nlm.nih.gov/pubmed/22607395 (2012)
[2255] http://www.ncbi.nlm.nih.gov/pubmed/21297087 (2010)
[2256] http://www.ncbi.nlm.nih.gov/pubmed/17412541 (2007)
[2257] http://www.ncbi.nlm.nih.gov/pubmed/12380884 (2002)
[2258] http://www.ncbi.nlm.nih.gov/pubmed/20825309 (2010)
[2259] http://www.ncbi.nlm.nih.gov/pubmed/9794683 (1998)
[2260] http://www.ncbi.nlm.nih.gov/pubmed/16222003 (2005)
[2261] http://www.ncbi.nlm.nih.gov/pubmed/8511813 (1993)
[2262] http://www.ncbi.nlm.nih.gov/pubmed/7784810 (1995)
[2263] http://www.ncbi.nlm.nih.gov/pubmed/9455520 (1998 *)
[2264] http://www.ncbi.nlm.nih.gov/pubmed/1569394 (1992)

- Seen with tetracyclines and penicillin[2265], ciprofloxacin[2266], sulfamethoxazole-trimethoprime[2267].
- Tachycardia, hypotension, and thrombocytopenia, elevated serum cardiac troponin[2268]

PO: I will often develop headaches (never have otherwise), dizziness, sore throat and cough from effective antibiotics, antivirals or probiotics – as well as much increased malaise.

26.1 Understanding and Managing JHR is Essential

I will get on a soap box here because I often have seen non-compliance with patients stopping a protocol due to JHR. A well controlled JHR results in patients becoming positive about the protocol and wishing to continue with the protocol. A few personal examples may help:

- In 2001, I was sick 24 hrs a day from starting doxycycline @ 3 times/day, but by day 5, I was out at the herx about 1 hr before the next dosage was due. Getting a few hours each day being productive and feeling better convinced me that antibiotics was the right path.
- In 2012, when I started E.Coli Nissle 1917, each day had a worst herx then the prior day. I was starting to seriously consider stopping. On day 3-4, I found my eyes tearing and suddenly realized that it had eliminated one dominant symptom – dry eye (and dry mouth disappeared a few days later). It would be two weeks before the JHR had reduced to give me 1 hr per day of productive time.
- Later in 2012 when I increased E.Coli Nissle 1917, I initially took it just before bed and had a horrible night including waking with a throat that felt like the Sahara at 3am. The next day I took it at noon and noted the symptoms that resulted and when they occurred. Nissle herx was very different then antibiotic herx. The result was to shift it until about 5 pm so that I would be awake to handle the intense dry mouth that showed up about an hour later.

There is no medical need to keep someone in a JHR continuously. A JHR, even for just 1 hr, is a positive sign suggesting that the treatment is appropriate. Jadin's practice of pulsing antibiotics likely help with patient compliance – they have a short sprint of JHR to endure and then some time to see their impact. I have seen this psychological benefit with someone doing a 5 day pulse of EDTA, by day 3 they were horrible but knowing that it would be just two more days kept them taking it.

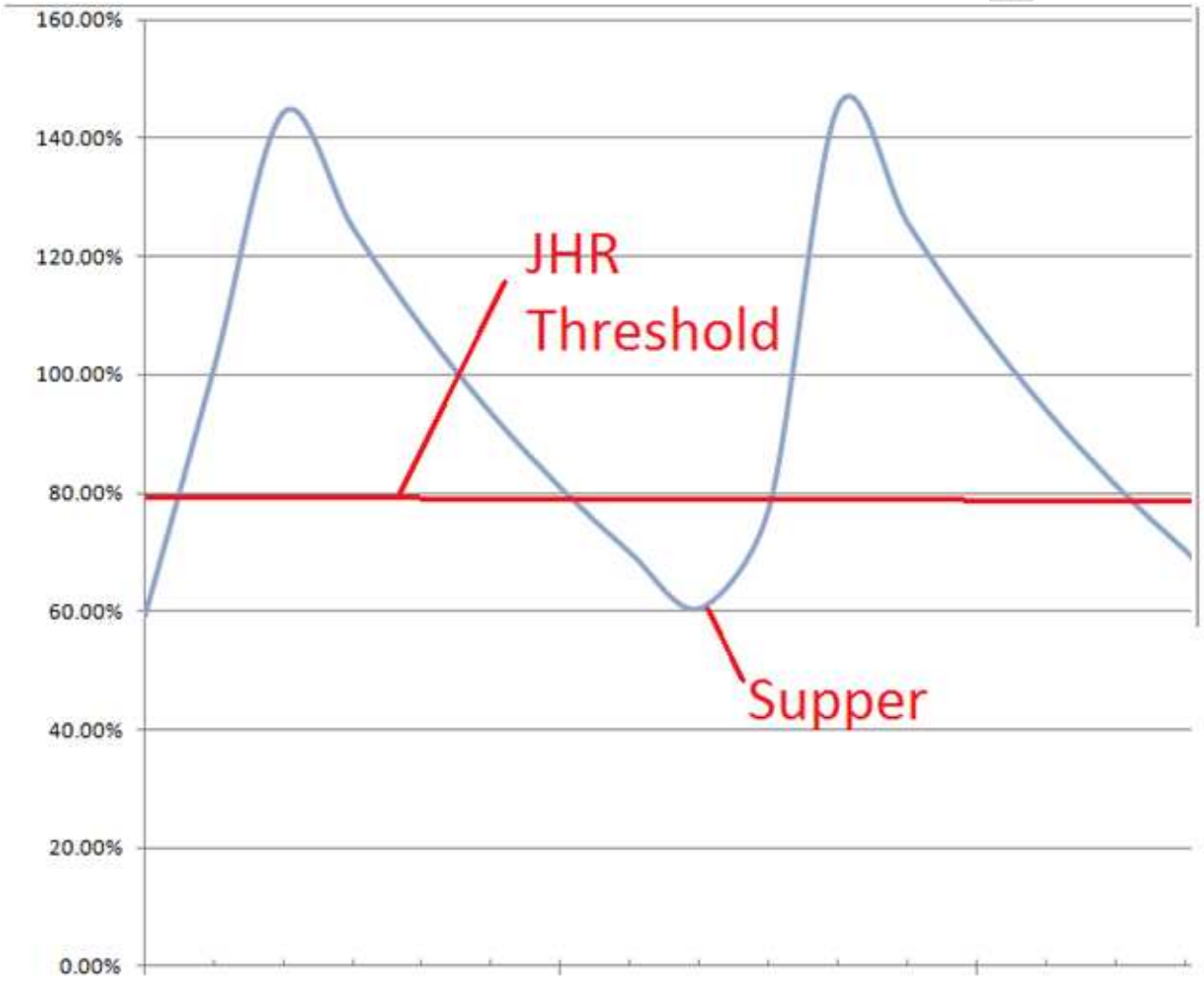
26.2 Managing JHR

In this appendix I will describe how I often manage JHR to reduce its impact on my day. Whenever I start an antibiotic, I avoid all potentators for 72 hours prior to start. I will attempt to find out the half-life of the antibiotic (time until the concentration is 50% less) and when the peak concentration after taking occurs (TMax). Peak concentration is generally delayed if taken with food. I use this information to schedule peak antibiotic concentration just *after* bed-time and then hope that I will sleep through most of any JHR. I will time things to have less JHR occurring during my waking day.

[2265] http://www.ncbi.nlm.nih.gov/pubmed/21803390 (2011)
[2266] http://www.ncbi.nlm.nih.gov/pubmed/12182387 (2002)
[2267] http://www.ncbi.nlm.nih.gov/pubmed/11721494 (2001)
[2268] http://www.ncbi.nlm.nih.gov/pubmed/22567483 (2011 *)

26.3 Basic Antibiotic JHR Curve

The curve below illustrates the concentration of an antibiotic over time. The first antibiotic is taken without food and results in TMax at 2 hrs, the second one with food with TMax at 4 hrs. At some concentration level, JHR is produced (shown as JHR Threshold on the chart). This level may change over time because JHR is not a direct result of the antibiotic, but a result of the volume of pathogens eliminated. As the volume of remaining pathogens drop, the line will raise. Eventually, there will be no apparent JHR resulting from the antibiotics. I term this event, the "1st level clearance of pathogens".



26.4 Potentated Antibiotic JHR Curve

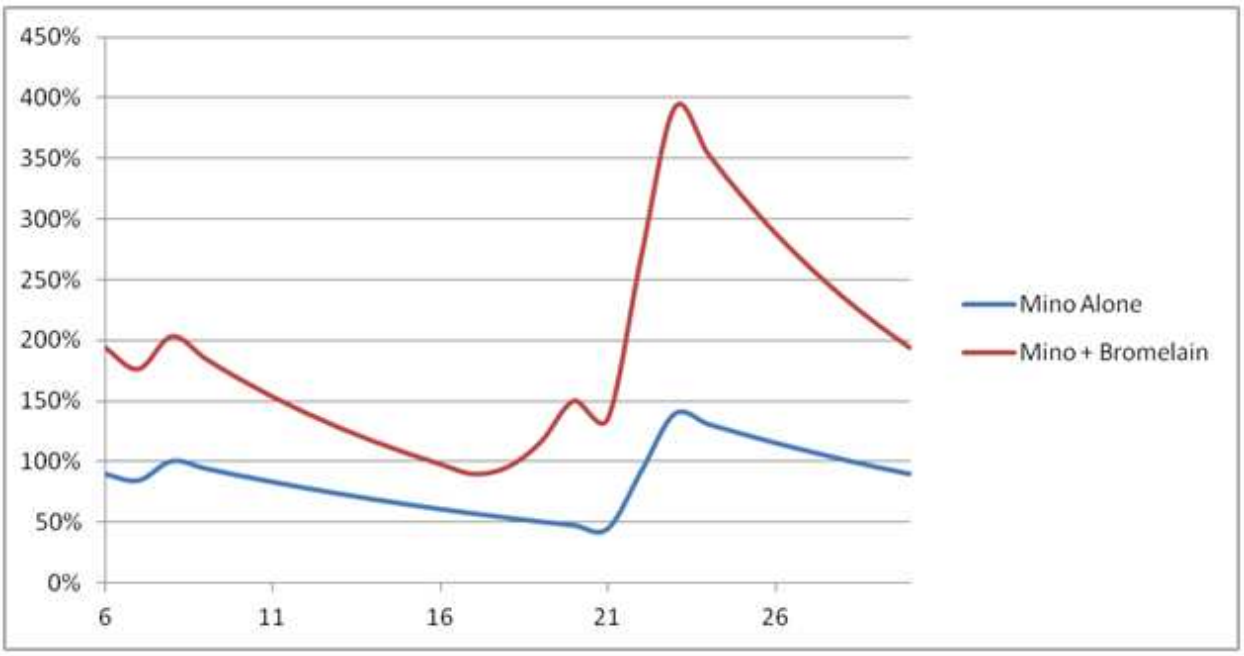
In the curve below we see how things change when a potentator is taken once a day (towards bed time). For example, taking 100 mg of minocycline twice a day and taking bromelain (which increases the penetration of minocycline by 220%[2269]) results in the following pattern:

- 100 mg at 6am

[2269] http://www.ncbi.nlm.nih.gov/pubmed/7001087 (1980)

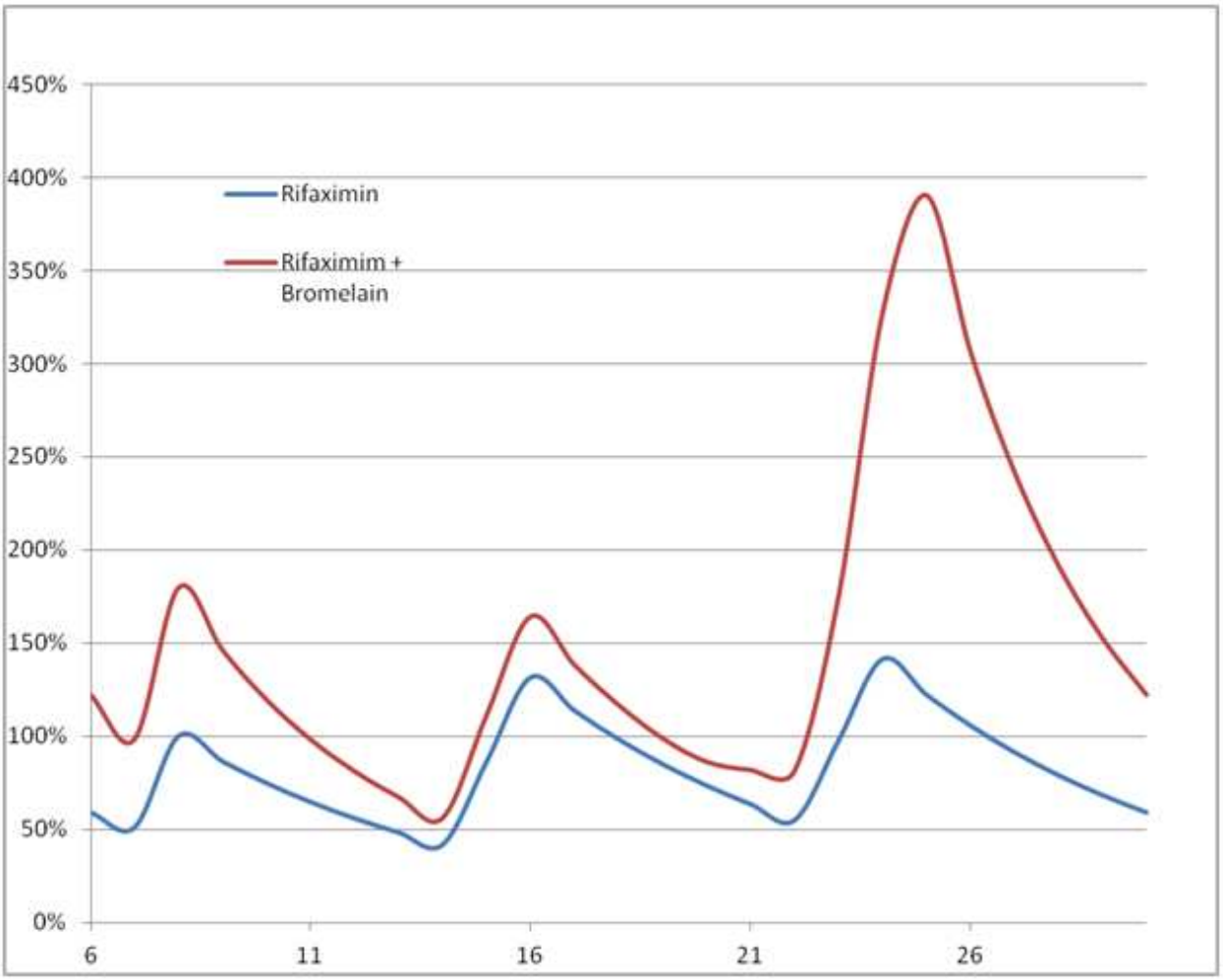
- 100 mg at 9pm
- Bromelain at 2pm

Doing some calculations in Excel, I ended up with the concentration charts shown below for minocycline during a day (6am until 6am the next day (30)). The result is a massive JHR while I sleep and a mild JHR during the day.



If your prescription is more often, then you will still see a similar pattern. For example, with a different antibiotic with three times a day, I calculated the following pattern (assuming similar amount of potentiating):

- 6 am – antibiotics
- 2 pm - antibiotics
- 10 pm - antibiotics
- 7 pm - bromelain



A rule of thumb is:

- Take the potentator 4-6 hrs before bedtime, once a day.
- Take the antibiotic 1 hr before bedtime.

26.5 JHR Times for common items

The table below shows the TMax and Half-Life for items that may cause a JHR. There are four classes of substances:

- Antibiotics
- Biofilms agents
- Potentators / Anticoagulation agents.

Combining their timing appropriately will allow you to manage the JHR better.

Substance	Time to Max Concentration (MaxT)	Half-Life
Amoxicillin[2270]		1 hr
Azithromycin[2271]		40 hr
Bromelain[2272]	1 hr	6-9 hrs
Clarithromycin[2273]		3 hr
Doxycycline[2274]	2.6 hr	16 hrs
EDTA[2275]		0.7 hr
Erythromycin[2276]		1 hr
Heparin[2277]	Immediate (injected)	1 hr
Levofloxacin[2278]	1 hr[2279]	6-8 hrs
Lumbrokinease[2280]		90 min
Minocycline[2281]	2 hr	11-23 hrs
NAC[2282]	2-3 hr	6 hr
Nattokinase[2283]		8 hrs
Rifampin[2284]	2 hr	5 hr
Serrapeptase	?	?
Tigecycline[2285]		37-67 hr

[2270] http://www.emedexpert.com/facts/amoxicillin-facts.shtml
[2271] http://www.emedexpert.com/compare/macrolides.shtml
[2272] http://nopr.niscair.res.in/bitstream/123456789/5694/1/NPR%207(4)%20359-363.pdf
[2273] http://www.emedexpert.com/compare/macrolides.shtml
[2274] http://www.drugs.com/pro/Doxycycline.html
[2275] https://www.medical-library.net/edta-chelation-therapy.html
[2276] http://www.emedexpert.com/compare/macrolides.shtml
[2277] http://en.wikipedia.org/wiki/Heparin
[2278] http://www.emedexpert.com/facts/levofloxacin-facts.shtml
[2279] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1315976/ (2005)
[2280] http://www.arrowheadhealthworks.com/bolouke.htm
[2281] http://www.drugs.com/pro/minocycline.html
[2282] http://www.benbest.com/nutrceut/NAC.html
[2283] http://www.cnmwellness.com/wp-content/uploads/2008/12/art_nattokinase_2.pdf
[2284] http://www.drugs.com/pro/xifaxan.html
[2285] http://aac.asm.org/content/49/1/220

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In Memory of

Richard A Van Konynenburg
A Great Friend and Researcher to the
ME/CFS, Lyme and MCS
Communities

Departed Sept 26, 2012

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