

DAIRY VETERINARY NEWSLETTER

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Repurposing of Drugs - Will This Provide More Effective Antimicrobial Therapy?

The first time I heard someone from a veterinary/food animal pharmaceutical company say that because of expense and regulations, we were not going to have a steady flow of new antibiotics being developed was approximately 15 years ago. I was not sure whether it was a commentary on regulations, a ploy, or a serious statement. Time has shown that whether from exhausted discovery of most of the antimicrobial compounds in existence, cost, regulatory burdens, other factors, or probably a combination of these, it is indeed the case that we have had few new antibiotic compounds brought to market for human or animal disease in recent years compared to the comparative explosion in antibiotic development from the 1940's through the 1990's.

There is considerable evidence that antimicrobial resistance among pathogens of food animals including dairy cows is not increasing as rapidly, and is not permanently maintained within bacterial species, as much as the popular press regarding this issue suggests that it is. Nevertheless, there is concern that human and animal bacterial pathogens are gaining resistance against multiple and additional classes of antibiotics.

Therefore, there is even more interest in developing new antimicrobial therapeutic compounds for use in animals and/or humans today than was evident several years ago. A phrase that has only come to my attention within the last 6 months or so is increasingly making its way into scientific literature and the dairy press: repurposing of existing drugs.

Repurposing of drugs - what is it?

Recently, several hundred non-antibiotic compounds that have traditionally been used for other reasons, for example antipsychotics or respiratory stimulants - have been screened for possible antimicrobial activity in mice. Some of this work was reported by Younis et al., in Current Pharmaceutical Design, December 2015. A library of 727 FDA approved drugs and small molecules was screened against the ESKAPE pathogen group (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter cloacae*). It is common that non-antibiotic drugs show bactericidal activity, but frequently the minimum inhibitory concentration (MIC) value is impossible to achieve in tissues of animals or humans, or the MIC cannot be reached safely. All 727 drugs were initially tested at the same concentration, 16 μ M, to identify those with antibacterial activity. Their MICs and minimum bactericidal concentrations (MBCs) were then determined according to the Clinical and Laboratory Standards Institute (CLSI). Initial screening found 24 (3%) of the 727 drugs active against MRSA and vancomycin-resistant *E. faecium*. However, only 2 drugs demonstrated MIC in clinically achievable ranges: Ebselen

(EB), an organoselenium compound that mimics glutathione peroxidase activity and is used as an antioxidant, and 5-fluoro-2'-deoxyuridine (FdU), an anticancer nucleoside drug.

8-week-old female BALB/c mice were inoculated intraperitoneally (IP) with 8×10^8 [colony forming units presumably; not specified] MRSA USA200. The term MRSA has historically referred to methicillin-resistant *S. aureus*, but is sometimes now used to abbreviate multiply resistant *S. aureus*, or sometimes just as a reference to multiply resistant “super bug” pathogens difficult to kill with almost all antibiotics. The paper refers to a table to explain what MRSA USA200 is, but a search for that term did not find it again anywhere in the paper. However, the paper did suggest that MRSA refers to methicillin-resistant *S. aureus*; this appears to be a reference strain.

The mice inoculated with MRSA were divided into 5 treatment groups: 3 doses of daily EB 30 mg/kg were either administered IP or orally to 2 groups. 3 doses of daily FdU 25 mg/kg were either administered IP or orally to 2 other groups. The remaining group consisted of untreated control mice. Mortality was monitored for 6 days, and the cumulative percent survival was calculated. Statistical analysis used Kaplan-Meier survival curves, and 95% confidence intervals were calculated.

EB oral treatment (not IP) significantly ($P = 0.003$) increased survival of mice (60%) compared to that of untreated controls (0%, all died within 5 days). For FdU, both oral and IP treatment significantly ($P \leq 0.001$) enhanced mouse survival (60% and 100%, respectively), compared to the same controls (0% survival). The full paper is available: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4686870/pdf/nihms709708.pdf>

Some of the authors' conclusions: “Repurposing FDA-approved drugs, with well-characterized toxicology and pharmacology, to find new applications outside the scope of the original medical indication is a novel way to reduce both the time and cost associated with antimicrobial innovation. - - Both drugs demonstrated potent bactericidal activity against clinical multi-drug-resistant staphylococcus isolates, including linezolid-resistant *S. aureus*, VRSA [vancomycin-resistant *S. aureus*], VISA [vancomycin-intermediate *S. aureus*] and MRSA.” (The paper did not describe the testing against any of those categories other than MRSA.) “ - - to date, no FDA-approved drug has been repurposed to treat bacterial infections. The non-antibiotic drugs that showed antimicrobial activity serve as [an] untapped reservoir for new antibiotic leads that could lead to identification of new targets which [could be] improved antimicrobial agents. The library we screened represents only 7% of the total drugs known to clinical medicine.”

Apparently following the mice for mortality for 6 days was considered long enough to ensure that those that survived for that long were unlikely to die from infection afterward. Keep in mind that all controls died by day 5 and the experiments were ended at day 6; I would like to have seen the survival time for the treated mice for longer than another day. It is obviously a big step from 6-day mouse trials to trials in food animals including dairy cattle, but it does indeed seem that evaluating non-antibiotic drugs such as EB and FdU for possible antibacterial activity may be an important area for future research that should be utilized. Research into repurposing drugs already approved for other reasons as antibacterial compounds is likely to continue.

Foot and Mouth Disease Vaccine Supply - Would a Vaccination and Ring Strategy Work?

Every year in the veterinary epidemiology course that I teach, we discuss Foot and Mouth Disease (FMD) as a classic example of foreign animal disease. We discuss many previous outbreaks around the world over the last 20 years, including outbreaks in Taiwan and the 2001 UK outbreak. Among other topics, we discuss in some detail the current controversy - ongoing for at least the last 15 years - regarding whether the U.S. should plan to attempt a test and slaughter eradication strategy or a vaccination and ring containment strategy in the event that FMD is introduced here.

It is worth noting that the U.S. working with Mexico in 1929 and 1952, and the UK in 1967 and 2001 are the only nations in the last 100 years to successfully eradicate FMD. This was accomplished using an eradication “stamp out” program in all 4 outbreaks. All other outbreaks that I can find information on, and there are quite a few, have resulted in FMD remaining as an endemic - and periodically becoming epidemic - disease in the affected countries. Many of these endemic countries use a vaccine strategy. However, during the last UK outbreak, the psychological toll on farm families was tremendous, and resulted in some producers whose herds or flocks were liquidated committing suicide.

Veterinarians and other livestock workers also sometimes found the work very stressful. In contrast, some producers who found the indemnity paid per animal slaughtered to be attractive urged veterinarians to declare their animals positive for FMD and have their herds or flocks depopulated. Therefore a vaccine strategy has been considered.

Should the U.S. plan for a vaccination and containment ring strategy in the event of an FMD outbreak?

By discussion and show of hands, each year the vast majority of the vet students support attempting a vaccination and ring strategy to control a potential FMD outbreak. They cite the psychology and bad publicity because of perceived poor animal welfare that accompany eradication efforts and favor the vaccine strategy. I can understand this opinion. However, can we obtain anywhere near enough doses of vaccine to realistically plan for a vaccination and containment ring strategy?

According to a report by J. Maday in Bovine Veterinarian, July 2015, FMD vaccine stocks are inadequate. During early July last year, “A coalition of agricultural organizations expressed serious concern that our current [FMD] vaccine bank and our ability to scale up vaccine production in an emergency are not adequate for addressing a medium to large FMD outbreak.” The entire article can be found at:

<http://www.bovinevetonline.com/news/industry/groups-call-improved-fmd-vaccine-stockpile>

“Currently, the USDA’s Animal and Plant Health Inspection Service (APHIS) manages a vaccine bank at Plum Island, NY, along with storage of vaccine antigen concentrate for a limited number of FMD strains. In the event of an outbreak, the antigen would be shipped to Pirbright, England or to Lyon, France where, under contract with Merial, it would be used to produce finished vaccine for shipment back to the United States. The program is currently funded at \$1.9M annually, and the groups say there is not enough vaccine available to handle an outbreak beyond a very small, localized event. The groups also note the turnaround time for vaccine delivery could involve weeks for even a small number of doses and months for the number of doses needed in a large outbreak.” (An important point that has also been made in recent years is that in the event of an FMD outbreak in at least one other country at the same time or just preceding as a U.S. outbreak, the English or French facilities would be faced with conflicting priorities besides only the needs for U.S. vaccine production.)

The article also mentions something that has complicated all efforts worldwide to control FMD with a vaccination strategy, always resulting in failure to eradicate. There are an estimated 25 serotypes of FMD virus, some affecting mainly hogs, some mainly sheep, some many different livestock species, and vaccination with an antigen from one FMD serotype is not cross-protective against different serotypes, or sometimes against other strains within the same serotype. The livestock group requested several things from USDA APHIS (Animal and Plant Health Inspection Service), all related to improving both the existing supplies and the response time to produce more of the needed FMD serotype vaccines in the event of an outbreak.

The decision is apparently being made right now

The subject of vaccination versus containment and availability of FMD vaccine is one that I have discussed several times with Dr. Barry Pittman, State Veterinarian of Utah. At this writing, he is at the Western States Livestock Health Association conference where state and APHIS livestock officials have decided that depopulation is “not doable” for the U.S. Logistics and workforce are the main reasons, but also the opinion prevails that the UK had too many negative publicity effects from depopulation. The response plan for any U.S. FMD outbreak is being changed to a “vaccinate to live” strategy. I asked Dr. Pittman about the fact that vaccination has never resulted in anything but endemic status, and the poor vaccine supply situation, which he has also been concerned about for years. He said that these challenges are being acknowledged, but the judgement has been made to go to a vaccination and ring plan for FMD control. Some interesting statistics from the conference:

- Estimated initial FMD vaccine supply: 2.5 million to 5 million doses (higher than any previous estimate)
- Iowa alone would request 20 million doses in an outbreak

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- Separate vaccines for each major FMD serotype exist now, no multivalent vaccines. 250 million total doses, divided across the different serotypes, is the current target for the entire U.S.
- 93 million cattle, 65 million domestic hogs in the U.S. (wildlife have not even been discussed yet in plans)
- 1 million hogs and 400,000 cattle move within the U.S. each day
- Tracking is completely inadequate now; major upgrades are needed (this has been said for at least 20 years)
- Testing to differentiate FMD vaccinates from naturally infected FMD animals is said to exist, but is not widely available to state labs yet

Dr. Pittman is doubtful that there will be a comment period; it seems that the decision is made. I suspect that if there is an outbreak, this plan will result in endemic FMD status, at least for many years. What do our readers think?

Please let us know your comments and also suggestions for future topics. I can be reached at (435) 760-3731 (Cell), (435) 797-1899 M-Tues, (435) 797-7120 W-F or David.Wilson@usu.edu.



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