

Early multidrug regimens in new potentially fatal medical problems

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The SARS-CoV-2 (COVID-19) pandemic has been the greatest challenge to medical practice in decades. We have witnessed fear, panic, confusion, division, and a wide array of regulatory and public health responses to the crisis ([National Institutes of Health, 2020](#)). We believe it is important for all physicians to keep in mind this pandemic is an emergency crisis and is not a usual context for drug development, guidelines, and recommendations for patient practice. In cardiovascular medicine we have had many disruptive forces as the field has evolved and we have witnessed reasonable responses with respect to pharmacotherapy when there was an absence of randomized trials to first guide the approach.

The working example in cardiology is the advent of bare metal coronary stents. Both authors can recall when these stents were first implanted, there was a well justified fear of catastrophic stent thrombosis and death generated from cases around the world. This is similar to COVID-19, where the reader is well aware that if left untreated, patients at high risk succumb far too often to hospitalization and death. The cardiology community did not leave a freshly stented patient untreated and wait for randomized trial "evidence" and US FDA approval to use drugs in this application. Some of the original multidrug protocols included full dose aspirin, dipyridamole, ticlopidine, warfarin, intravenous heparin, and intravenous dextran ([Arrozza and Baim, 1995](#)). This super anticoagulant regimen came at a heavy cost of bleeding complications but was felt justified given the risk of fatal stent thrombosis. Over time, many randomized trials were carried out and the reports progressively refined the approach. Today a patient who undergoes elective percutaneous coronary revascularization with drug eluting stents is in the hospital a few hours and is discharged on aspirin 81 mg and clopidogrel 75 mg daily. The reader can appreciate how it took many years of trials to arrive at this streamlined, affordable, and evidence-based approach.

As we sit here today, an ambulatory patient age 75 with obesity, diabetes, and heart disease faces a 20% risk of hospitalization and death with COVID-19. This risk is far greater than the early era patient faced for fatal stent thrombosis. There is no doubt that early sequential multidrug therapy for COVID-19 with 2 or more anti-infectives (hydroxychloroquine, ivermectin, favipir-

ravir, azithromycin, doxycycline) followed by corticosteroids if pulmonary symptoms develop and in most high-risk cases full dose aspirin and oral novel anticoagulants or subcutaneous low-molecular weight heparin are all medical necessary and clinically indicated to prevent hospitalization and death ([McCullough et al., 2020](#)). There are additional nutraceuticals (zinc, vitamin D, vitamin C, quercetin) which are all safe and helpful in COVID-19 treatment ([McCullough et al., 2020](#)). Just as in early post-stent management, these multi-drug regimens given the historical context and the lethality of the condition should not be delayed for more evidence or because of unjustified safety concerns. As internists and cardiologists we have always acted decisively for our patients best interests first and have been willing to adjust and modify our approach as the randomized trials report typically over many years.

There are no conclusive randomized trials for any therapy in COVID-19. Such trials would need to have > 20,000 patients and ~5% event rates to give stable point estimates, confidence intervals, *P*-values, and robust event differences. These criteria have not been met for any drug including remdesivir, dexamethasone, convalescent plasma, bamlanivimab, or COVID-19 vaccines. Doctors must use both the art and the science of medicine to save lives in COVID-19. At the present, contemporary management of this crisis is more of an art based on clinical judgement which has great variation from doctor to doctor depending skill in interpreting the medical literature. Just as in the prevention of stent thrombosis, we must act decisively to save lives and avoid being paralyzed by confusion and opinions regarding efficacy and safety of any single drug.

Authors' contributions

Dr. McCullough drafted the paper and Dr. Oskoui provided edits.

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Conflict of interest

The authors declare no conflicts of interest statement.

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