According to ancient mythology, the peasant Gordius, who married the fertility goddess Cybele, became king of Phrygia. He then dedicated his chariot to Zeus in the city Gordium and fastened it to a column with a large, complicated knot that became known as the Gordian knot. An oracle predicted that the future king of Asia would be the only person who could disentangle this knot.

Many individuals who traveled to Gordium attempted to untie the knot and thereby lay their claim to the throne, but their attempts proved futile. Then the Greek conqueror, Alexander the Great, whose actual name was Alexander III of Macedon, visited the city in 333 BCE. He, too, was perplexed as he studied the knot, searching for its hidden ends. Whether prompted by impatience or insight, Alexander unexpectedly unsheathed his sword and sliced through the strands of rope, thereby severing and removing the knot. He subsequently conquered Asia, fulfilling the prophecy. He founded more than 70 cities and created a vast empire across three continents before his death in Babylon in June 323 BCE.

Alexander’s bold, unexpected resolution gave rise to the oft-repeated saying, “cutting the Gordian knot.” That saying—now ubiquitously and inevitably linked to the shopworn notion of “thinking outside the box”—continues,
Researchers found that a high proportion of swine-pathogenic *Escherichia coli* in Japan are resistant to colistin and noted concern for “a risk for transmission of *mcr-1* from these strains to human-pathogenic bacteria.” A recently published report describes a patient in the United States infected with *E. coli* containing the *mcr-1* resistance gene on a plasmid conferring resistance to colistin, the current antibiotic of last resort for treating patients with infections caused by some multidrug-resistant bacteria. Like Zeus, Fleming knew this day would come.

Some of the overlapping strands woven into the Gordian knot of antimicrobial resistance are myriad mutations and adaptations of various infectious organisms, lack of development of new antimicrobial agents, modern agricultural practice, and ineffective antibiotic stewardship. Tackling individual problems such as multidrug-resistant *Shigella* sp. infections, antibiotic overuse, or the transition of *Clostridium difficile* and *Staphylococcus aureus* from institutionally acquired to community-acquired infections is vital because an all-encompassing solution to the puzzle, such as that found by Alexander the Great, does not seem to be on our horizon.

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