Evolution of Staphylococcus aureus Following the Introduction of Antibiotic Therapy

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Introduction

"Without innovative public policy and additional financial support, fewer and fewer antibiotics will be available to treat the increasing number of drug-resistant and dangerous microbes that threaten Americans and the global community."

– Infectious Diseases Society of America

Staphylococcus aureus is a species of bacteria which colonizes the human respiratory system and skin in a commensal relationship. Although generally harmless, S. aureus can be responsible for a variety of diseases including food poisoning, necrotizing pneumonia, and endocarditis[1]. It is among the most common causes of nosocomial infections worldwide, accounting for some 500,000 nosocomial infections per year in America alone. About 20% of the world’s population is colonized with S. aureus long term, with an additional 60% of the population will host a colony at some point during their life[2].

S. aureus infections can usually be treated with antibiotics of the penicillin family, the discovery of which is accredited to Alexander Fleming in 1928 when a culture of Penicillium rubens was observed excreting a substance with antibiotic properties. By 1945, penicillin was being mass produced for medical use[3], but within a decade populations of S. aureus were showing increasing resistance to what had previously been considered a miracle drug. In 1952, methicillin (renamed meticillin in 2005) was introduced as an alternative antibiotic due to the increasing rate of penicillin resistance in S. aureus[4], but by 1961 British physicians were reporting S. aureus isolates which had acquired resistance to methicillin[5]. This methicillin-resistant S. aureus (MRSA) now composes as much as 67% of the S. aureus colonies in developed countries such as the U.S. and Great Britain[6]. Furthermore, MRSA has become synonymous with multidrug-resistance due to a tendency for MRSA isolates to be resistant to the majority of commonly used antibiotics[2].

Another antibiotic, vancomycin, was discovered soon after penicillin, but was rarely used because other antibiotics were considered more efficacious and less toxic until the 1980s when it became the drug of last resort for treating MRSA[7]. S. aureus proved slow to develop resistance to this antibiotic, allowing it to be used safely for nearly 30 years before vancomycin-resistant S. aureus (VRSA) isolates were identified.

Staphylococcus aureus is a unique species of microbe which has lived alongside mankind since before recorded history. In addition to an intimate familiarity with its host's body, this bacteria is capable of rapidly evolving to withstand an ever increasing arsenal of manmade antibiotics. Against this worthy foe mankind is engaged in an arms race: modern medicine against evolution.

The recent evolution of S. aureus can be categorized as the development of a range of antibiotic resistances, from penicillin to methicillin to vancomycin, accentuated by a series of epidemic outbreaks. As multidrug-resistant S. aureus spreads from hospitals to communities to the food chain, researchers struggle to stay ahead of one of our oldest companions.

History of Staphylococcus aureus

“It knows how to live on inanimate objects, in our noses, in our skin, in our genitals. It’s virulent, it’s adaptive, and it is able to circumvent almost everything we throw at it. It is a perfect pathogen.”

– Dr. Robert Daum, M.D.

Staphylococcus aureus is among mankind’s oldest evolutionary companions, benignly colonizing human hosts for hundreds of thousands of years. This commensal relationship is generally harmless to humans, but certain conditions can lead to the bacteria attacking its host, resulting in a wide range of infections, from pimples and rashes to pneumonia, toxic shock, and bone abscesses. These infections are particularly dangerous because of S. aureus’ familiarity with the human immune system: having colonized mankind for so long, S. aureus has developed a huge range of virulence factors – over 70 enzymes and toxins capable of destroying cells, more than any other species of bacteria[8].

In addition to being extremely virulent, S. aureus has proven to be capable of adapting quickly enough to overcome any new threat. It began developing defenses against penicillin as soon as initial testing began on the drug, forcing the pharmaceutical industry to develop a new drug, methicillin, less than a decade after the introduction of the first antibiotics to medicine[4]. With an atomic structure unlike anything occurring in nature, methicillin was expected to effectively combat S. aureus for decades, allowing ample time to develop the next generation of antibiotics. This miracle drug, developed in 1952, became widely used in 1960. By 1961, S. aureus had developed methicillin resistance[4][5][8].

Methicillin resistance in Staphylococcus aureus was first documented in Great Britain in 1961, two years after the drug was licensed for use in England. In 1968, MRSA strains began to be identified in the United States at the Boston City Hospital in Massachusetts. At this time MRSA isolates were only identified as being acquired in clinical environments, due primarily to the limit of antibacterial use to hospital settings. Over the next 30
years the percentage of \textit{S. aureus} infections identified as MRSA increased slowly but steadily, but remained attributed to clinical environments. By 1998 occurrence rates of Healthcare-Associated MRSA (HA-MRSA) had stabilized.

Although the occurrence rates of HA-MRSA had stabilized, 1998 also marks the beginning of the “second epidemic”: the development of MRSA infections from the community. This Community-Associated MRSA (CA-MRSA) was first documented in 1996 by Dr. Robert Daum of the University of Chicago. Daum had noticed a spike in instances of children being admitted to the Wyler Children’s Hospital with MRSA infections, and a survey of the children’s records had uncovered an anomaly: none of the infected children had recent contact with an environment where MRSA infection was expected. The strain the children had acquired was as virulent as the HA-MRSA the doctors had grown accustomed to, but resistant to fewer antibiotics, suggesting a more recent evolutionary development of methicillin resistance\cite{8,9}.

Daum’s team of researchers isolated samples of \textit{S. aureus} from two of the children who had been admitted with MRSA and used pulsed-field gel electrophoresis (PFGE) to compare them with older samples of HA-MRSA. The results (figure, right) showed that the MRSA of the two children (lanes 5 and 6) were genetically identical and distinct from any of the samples taken from previous patients, despite the children being admitted 6 months apart, with no contact to each other\cite{8}. Despite this evidence, Daum’s findings were rejected by the medical community. It took two years for the \textit{Journal of the American Medical Association} to publish the findings, along with an editorial which suggested that the research was fundamentally flawed and should be disregarded.

The opinion of the \textit{JAMA} was shared by a majority of the medical community. There had been only one other well-documented case of a MRSA outbreak in the community, in 1980 when over 100 Detroit drug addicts acquired infections in under two years. An investigation into the outbreak concluded that one of the infected individuals had acquired the MRSA strain at the Henry Ford Hospital and spread it throughout the community. Since the outbreak was limited to individuals with weakened immune systems, this incident was considered evidence that MRSA could not survive for an extended period outside of hospitals, as it would eventually succumb to the strong defense of healthy immune systems\cite{8}.

While there were a few additional reports of new MRSA variants appearing sporadically, the medical establishment had already dismissed the possibility of MRSA spreading outside of hospitals and clinics\cite{8}.

Community-Associated MRSA (CA-MRSA) started appearing more frequently. By 2005 CA-MRSA was occurring regularly in groups of individuals sharing close quarters: athletes, military units, urban children, and prisoners. By 2006, 67% of \textit{S. aureus} colonies in developed countries displayed resistance to methicillin\cite{6}. The medical establishment eventually accepted the fact that CA-MRSA was a legitimate threat, but while the medical community was slow to accept change \textit{S. aureus} had continued to evolve.

Patients suffering the most extreme MRSA infections were being treated with vancomycin, a glycopeptide antibiotic administered intravenously and used only when all other treatments had failed. The complex molecular structure of this antibiotic, combined with sparing use, prevented \textit{S. aureus} from quickly developing resistance, but in 1998 researchers began documenting colonies of \textit{S. aureus} with varying degrees of vancomycin resistance\cite{10}. This newly discovered Vancomycin-Resistant \textit{S. aureus} (VRSA) was unaffected by all but the newest and most powerful antibiotics, but Vancomycin-Intermediate \textit{S. aureus} (VISA) has proven to be even more difficult to treat\cite{8}.

The danger presented by Vancomycin-Intermediate \textit{S. aureus} (VISA) is the insidious nature of its vancomycin resistance. VISA colonies are not strongly resistant to vancomycin. Instead the term is applied to colonies which appear to be susceptible to normal doses of vancomycin while hosting smaller colonies with enough resistance to survive treatment. Administration of vancomycin treatment successfully kills the susceptible portion of the colony, reducing competition for the more resistant strains\cite{8}. While these more resistant strains may be susceptible to higher doses, the adverse side effects associated with vancomycin (including kidney damage and deafness) make such dosage increases dangerous for the patient.

With \textit{S. aureus} developing resistance to vancomycin, new, novel antibiotics are being developed to treat the most extreme infections. Unfortunately, by the time new antibiotics become available to the medical community resistance is already being reported by the pharmaceutical developers\cite{11}. Staph is evolving as quickly as modern medicine can develop new treatments.

**Agricultural MRSA**

“The extensive use of antimicrobials for prevention of disease appears to be an important risk factor for the spread of MRSA.”

- European Medicines Agency

In July 2004 a new strain of MRSA was detected in a Dutch toddler. Her parents and sister tested positive for this new strain, leading researchers to a more in-depth investigation into the origin of the strain. Almost a quarter of the family’s friends were identified as carriers of this
novel MRSA strain, including all pig farmers with whom they were close acquaintances. This association led to the final breakthrough: the fact that 3% of pig raised by the individuals tested were infected with MRSA[8].

The newly identified Dutch "pig MRSA," named ST398, was unique among S. aureus isolates: the genetic structure was distinct from hospital-associated MRSA, and there had been no previously identified community-associated MRSA in the Netherlands. As with every other MRSA strain, ST398 displayed a strong resistance to the penicillin family of human antibiotics, however it had also acquired a unique resistance to the antibiotics approved only for livestock use[8]. While MRSA had been identified in cows as early as 1972, there had never been an incident of livestock MRSA colonizing a human host[13].

ST398 was initially identified as a pure livestock strain, having evolved in pigs before being transmitted to Dutch farmers. More recently, researchers used full-genome sequencing typing to 89 variants of the ST398 strain, concluding that the strain identified in the Netherlands was derived from a human S. aureus ancestor. Such a recent ancestral lineage suggests that S. aureus spread from humans to livestock and subsequently acquired the SCCmec cassette responsible for methicillin resistance[13]. Heavy use of livestock antibiotics resulted in strong selective pressure favoring additional antibiotic resistances before ST398 was reintroduced to its original host.

The 2004 farm outbreak marks the beginning of the "third outbreak." Patients without any livestock contact were infected with ST398 by 2005. In 2007 the pathogen was spreading through hospitals and nursing homes. By 2010 ST398 had spread to across Europe and into North America. A survey of livestock in Iowa and Illinois revealed that 49% of pigs and 45% of farm workers were colonized with ST398[8].

Vaccination: An Ultimate Solution?

“This organism has multiple strategies for accomplishing all its tasks, from invading the blood stream to elaborating toxins to causing local skin abscesses. Targeting a vaccine against just one of them merely eggs the bug on.”

- Dr. Robert Daum, M.D.

S. aureus has proven capable of developing resistance to new antibiotics so quickly that major pharmaceutical companies are refusing to develop drugs, arguing that the pathogen undermines new compounds so quickly that they cannot recoup the costs of development[13]. Many of the larger pharmaceutical companies have shifted focus to the development of a MRSA vaccine.

All modern vaccinations are derived from the same theory: by introducing an antigen to the body, the immune system can learn to combat the pathogen effectively enough that the infection cannot establish a foothold. This strategy is remarkably effective in flu and chickenpox vaccines, where the antigen is a weakened form of the virus, allowing the body to produce an antibody which will protect it from future infection. The presence of these antibodies usually signifies immunity to the target pathogen, and the Food and Drug Administration requires vaccines to demonstrate antibody production in order to gain approval[13]. However, increased levels of antibodies in victims of severe S. aureus infections show no increase in resistance to the pathogen, and sometimes appear signify greater susceptibility to future infection[13].

All recent attempts to develop a S. aureus vaccine using the normal strategy have failed, but a rare condition called Hyperimmunoglobulin E syndrome (HIES) or Job’s syndrome may reveal a new strategy[13]. Individuals with HIES are unable to produce immune cells called T17 cells, which results in chronic S. aureus infections. Since the presence of these cells is what apparently prevents the kind of chronic infections that characterize HIES, increased T17 levels may result in increased resistance to S. aureus, even to the point of practical immunity.

S. aureus, however, is a versatile pathogen which has proven capable of adapting to every new method of control. Even a successful vaccine might be overcome, Daum argues, if it does not combat the bacteria with multiple methods[13].

Conclusion

"Meticulous attention to infection-control practices is of paramount importance in preventing MRSA colonization."

- Dr. Evelina Tacconelli, M.D.

Mankind’s rivalry with Staphylococcus aureus is as old as time itself, but direct conflict is a recent development. The discovery of antibiotics in the early 20th century was hailed as the final victory over disease, but S. aureus was already evolving methods to overcome the new drugs. New antibiotics were developed, forcing S. aureus to develop new resistances. Doctors, will full faith in their advanced medical techniques, prescribed antibiotics as prophylactics. This overuse of antibiotics resulted in increased selective pressure for multidrug-resistance in S. aureus, eventually leading to multiple, independent, and geographically distinct developments of MRSA strains.

Doctors are now aware of the dangers of antibiotic overuse, but with new S. aureus isolates displaying new resistance to even the most novel antibiotics it may be too little, too late. The next battle in mankind’s war on disease is the development of a functional vaccine to protect against the distinct illnesses caused by S. aureus, but the bacteria has proven capable of circumventing every vaccination method proven effective against less versatile pathogens.
Where modern medicine falls short, simple sanitation methods can offer a way to prevent *S. aureus* colonization. Washing the hands with soap and water has proven effective in preventing *S. aureus* transmission, and bathing in a dilute chlorine bleach mixture is a common and effective home remedy for minor MRSA infections.

**Bibliography**


