

Bacterial infections

What are bacterial infections?

Bacteria are microscopic organisms of many different types with a chemically distinctive cell wall. This membrane confers a particular shape on each type: spherical, rod-shaped or spiral. They multiply by cell division, a process that can occur every 20-30 minutes. A single bacterium entering the body and multiplying at this rate could give rise to over 30 billion new cells within 12 hours. Fortunately, most bacteria are harmless and some are even essential, such as those in the intestine which aid digestion.



But a minority, called pathogens, cause disease. These may be localised near the surface of the skin, as in acne, laryngitis, boils and abscesses, or invade internal organs and cause, for example, serious and life-threatening infections of the urinary tract (prostatitis), brain (meningitis) lung (pneumonia), heart (endocarditis), or bloodstream (septicaemia).

Who do bacterial infections affect?

Everyone experiences bacterial infections from time to time, but most heal by themselves or are readily treated with antibiotics. However, resistance to antibiotics is a growing problem and infections that were treatable a decade ago are staging a comeback. For example, tuberculosis has staged a marked resurgence in various forms and is more often drug-resistant than before.

Traditionally, methicillin-resistant *Staphylococcus aureus* (MRSA) infections occurred exclusively in hospitals and were limited to immunocompromised patients or individuals with predisposing risk factors. Recently, however, there have been alarming reports on community-associated MRSA strains, which cause severe infections that result in necrotizing fasciitis or even death in otherwise healthy adults outside of healthcare settings.

Bacterial infections are caused by many different microorganisms.

A lot of agents have been developed to treat bacterial infections, but resistance to them is a major problem. The pharmaceutical industry is working to develop new classes of antibiotics. By staying one step ahead, it is hoped that fewer and fewer people will die of infection.

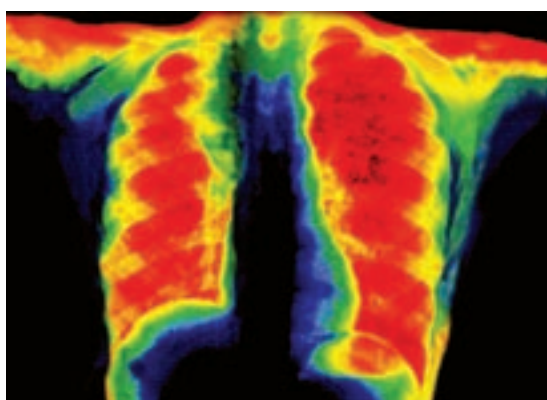
People, whose immunity is depressed by illnesses such as cancer, or suppressed as in transplantation, are at greater risk of serious infection. As more patients are treated, hospital-acquired infections - after surgery, intensive care treatment or on prolonged catheterisation - are increasing. If septicaemia develops, it may lead to septic shock: a cascade of systemic inflammation, coagulation, and low blood pressure with a sometimes fatal outcome through multiple organ failure.

Present treatments:

Many antibiotics have been discovered over the past 60 years, including the synthetic penicillins and cephalosporins, tetracyclines, macrolides, the aminoglycosides, i.e. the streptomycin group, and quinolones. The latter inhibit the bacterial enzyme gyrase and are another option to treat pneumonia and infections of the urogenital tract.

Despite this range of agents, the loss of efficacy in the face of resistant organisms such as MRSA and vancomycin-resistant enterococci (VRE) is creating widespread concern among clinicians. In an attempt to keep ahead of growing resistance, a variety of antibiotics have been introduced in recent years.

The combination of two compounds of the 'streptogramin' group contains two structurally different components that together kill a wide range of bacteria, including MRSA strains. Another avenue is an oxazolidinone derivative which is valuable in treating skin and soft tissue infections in hospitals where multiply resistant strains are likely to be present.



Novel broad-spectrum cephalosporin antibiotics have been developed to treat skin and skin structure infections. The ketolides are another new class of antibiotics. They are intended for the treatment of respiratory tract infections, including resistant strains of *streptococcus pneumoniae*. They may turn out to have useful activity against some less usual pathogens such as *Chlamydia*, mycobacteria, the protozoan *Toxoplasma gondii*, which causes opportunistic infections in HIV / AIDS patients, and *Legionella pneumoniae*, the cause of Legionnaires' disease.

Perhaps the advance in research that has been exciting clinicians most is the promise of an effective treatment for severe septicaemia or sepsis, for which there were no medicines authorised. An agent that has raised hopes is a recombinant version of the naturally occurring activated Protein C. This compound reduces the inflammation and blood clotting associated with sepsis and has been demonstrated to reduce the death rate from severe sepsis by about 20 per cent.

What's in the development pipeline?

New antibiotics belonging to a variety of different classes are in advanced clinical development. Even tetracyclines which consist of four consecutively fused carbon rings, labelled A through D, are still being studied. Scientific reports underscore that D-ring variations have shown particular promise against resistant bacteria. New carbapenem antibiotics are being developed for either oral administration or for parenteral treatment of community-acquired infections.

Scientists are studying a molecule in Phase 3 which is first in the class of pleuromutillin antibiotics, while two further members of this class are in Phase 1 development. The preparation is applied to the skin in skin and soft tissue infections. Another class of medicines which are studied in complicated skin and skin structure infections are the lipoglycopeptides. Other new antibiotics under development for skin infections include a dihydrofolate reductase inhibitor.

Another class of antibiotics under research is the glycyclines, which are related to the tetracyclines. There is an injectable compound of this type in late-phase development. It has activity against a broad spectrum of bacterial strains, including those that are resistant to tetracyclines. Further antibiotics that are advanced in the clinic include a compound which belongs to the class of oxazolidinones.

Of particular interest are new treatments for the serious problem of diarrhoea caused by *Clostridium difficile*. Two new compounds under development are a lipoglycopeptide that acts to kill the bacteria in the intestine and a non-absorbed polymer to bind the toxins released by this organism. Another toxin-binding approach is being explored in Phase 2 with a monoclonal antibody against *C. difficile*.

Compounds in clinical development for severe sepsis are all targeted to shut down the cascade of events that lead to circulatory collapse and organ failure. These include an anti-tumour-necrosis-factor (TNF) monoclonal antibody, a tissue factor pathway inhibitor, a nitric oxide-production-inhibitor and a recombinant platelet-activation-factor (PAF) inhibitor. A monoclonal antibody directed against Factor IX is also in clinical trial for sepsis.

The longer-term future:

Hopes of overcoming antibiotic resistance in the future must be pinned on molecular biologists that are sequencing the genes in common pathogens. In the bacterial cell, the ribosome is the main target for antibiotics that inhibit protein biosynthesis. Structurally and functionally critical sites in the ribosome may be used as new antibiotic targets. By mapping recombinant RNA sites where nucleotide alterations impair the ribosome function or assembly, researchers have located a number of mutations in previously unexplored regions which are considered as new targets for antibiotic treatment.

Scientists have also been able to reveal previously uncharacterised *S. aureus* virulence factors. Apparently, MRSA strains secrete staphylococcal peptides that have the ability to recruit, activate and subsequently destroy the human white blood cells known as neutrophils, thus eliminating the main cellular defence line against *S. aureus* infection.

Furthermore, research groups have published encouraging results on a new compound which has been found in bacteria isolated from South African soil. The molecule binds to the enzyme FabF that catalyzes a key pathway in the synthesis of fatty acids, necessary components for the synthesis of the bacterial cell membrane and its surface. However, such approaches are still experimental.

Until the finding of new avenues, the greatest vigilance in clinical use of the existing spectrum of substances needs to be observed, in order that the lifetimes of those antibiotics that are currently available and effective are not prematurely shortened.

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