POINT-OF-CARE METHODS CAN CURB DEVELOPMENT OF ANTIBIOTIC RESISTANCE

BETTER CLINICAL DECISIONS WITH POINT-OF-CARE METHODS CAN CURB DEVELOPMENT OF ANTIBIOTIC RESISTANCE

MIRACLE DRUG THAT SHOULD BE PRESCRIBED WITH CAUTION

Before the 1940s, bacterial infections were far from trivial. Not seldom they had lethal outcome. When penicillin, discovered by Ian Fleming in 1928, came in to use, bacterial infections were no longer the serious threat to life and health they had previously been. By now it has saved hundreds of millions of people from infectious diseases.

Antibiotics are taken for granted as part of our modern life and have been viewed as miracle drugs that could be prescribed without risks. It, however, didn't take more than four years after the start of mass-production of penicillin in 1943, before the first penicillin-resistant bacteria strain showed up. This strain, Staphylococcus aureus, has since then been accompanied by a large number of other drug-resistant strains; now not only resistant to penicillin but also to other types of antibiotics. In later years, the problem of multi-resistant strains has put considerable pressure on healthcare by limiting the availability of treatment options. The loss of effective antibiotics is now a problem of global dimension that affects us all.

RESISTANCE TO ANTIBIOTIC DRUGS HAS TURNED INTO A GLOBAL RISK

Infections caused by resistant bacteria can have serious consequences from protracted hospitalization to increased mortality. Most deaths caused by pneumonia in children under the age of five are due to a lack of access to effective antibiotics[1] and an estimated more than 200 000 neonatal deaths are attributable to resistant pathogens each year.[2] Low-income countries are particularly severely affected because the spread of resistant bacteria is facilitated by poor hygiene and limited access of clean water and sewage facilities, overcrowding, contaminated food and susceptibility to infection.

Antibiotic-resistant bacteria spread in just the same ways as other bacteria. That is, they are transferred between people, animals and foodstuffs, and they can spread in the environment. Therefore, being a multisectoral problem, the efforts to combat further development of antibiotic resistance, have to be made from a broad perspective. The World Economic Forum has identified antibiotic resistance as a global risk beyond the capacity of any organization or nation to manage or mitigate alone.

INCREASING USE OF ANTIBIOTICS WORLDWIDE

Even though antibiotic resistance is a global problem, variations in antibiotic resistance across countries are, at least partly, attributable to variations in volumes and patterns of antibiotic consumption.[3] One of the culprits in the development of antibiotic resistance is the over-use of antibiotics in medicine. Between 2000 and 2010, the consumption of antibiotic drugs increased by 35 %. The largest part, 76 % of the total increase, was attributable to the BRICS countries, that is Brazil, Russia, India, China and South Africa, although their share in the overall increase in global population was only 31 %. Per capita the consumption of antibiotics is highest in India and second highest in China. The USA has the world's third largest consumption whereas in other high-income countries, the consumption varies considerably despite similar economic development.[4] In Europe, the consumption of antibiotics varies across regions. It is highest in the south, moderate in eastern parts and lowest in the north. In addition to the higher consumption in eastern and southern parts the seasonal variation is also greater in these areas as compared to the northern countries, indicating unnecessary usage for viral infections.[3] Although increased access to antibiotics for individuals who were previously unable to afford these life-saving drugs is undoubtedly positive, many broad-spectrum antibiotics are now sold over-the-counter without a documented medical need. Self-medication by consumers with antibiotics purchased without a prescription is common, especially in eastern and southern Europe, Africa, South America and Asia.[4, 5]

In the close to hundred years of antibiotic treatment, antibiotic resistance has by now turned in to a threat to global health. The consumption of antibiotics increases worldwide. Some patients are prescribed unnecessary courses of antibiotics, whereas others are still not given appropriate treatment. If we want long-term solutions we need to use antibiotics wisely in order to conserve the antibiotics now in use. The resistance problem has to be managed and mitigated from a broad perspective addressing the challenge of access and rational use.

RESPIRATORY TRACT INFECTIONS THE MOST COMMON CAUSE FOR A CALL AT THE DOCTOR'S OFFICE

Most of the antibiotics used in medicine are, however, prescribed by general practitioners, and primary care accounts for 80–90 % of all antibiotic prescriptions in Europe.[6] The most common patient in primary care is a person presenting with a respiratory tract infection, and most antibiotics are prescribed to treat this condition. Clinical signs are often ambiguous and difficult to rely on to discriminate between viral and bacterial infections. One strategy that has been suggested to decrease use of antibiotics is "delayed antibiotics". The patient is given a prescription for antibiotics but is advised to delay start of treatment for 48 to 72 hours in the hope that the symptoms will resolve. A Cochrane review on delayed antibiotics for respiratory tract infections showed a significant reduction in antibiotic use compared to immediate antibiotics. There was no difference in clinical outcomes for cough and common cold. Only in acute otis media and sore throat immediate antibiotics were more effective for the symptoms fever, pain and malaise. The patients, however, preferred immediate antibiotics.[7] Maybe this can be partly attributed to a public misunderstanding as to what antibiotics are effective for. According to a World Health Organization (WHO) survey across 12 countries, 64 % of the public believe that antibiotics work also for viral infections such as influenza and colds.[8]

DIAGNOSTIC UNCERTAINTY PROMOTES ANTIBIOTIC OVERUSE

Diagnostic uncertainty, not being able to decide whether an infection has viral or bacterial cause, makes it difficult for clinicians to know when to provide antibiotics and when not to. The result of this uncertainty, possibly also in combination with pressure from the patient, is often a "just-in-case-prescription".

There are different methods to help clinicians with diagnosing infections. Traditionally, the gold standard for identification of pathogens has been culture-based approaches requiring microbiological laboratory facilities. Culturing is a slow procedure – pathogens are at best identified in 24 hours. Attempts have been made to reduce testing time with other type of methods based on for example PCR-technique and mass spectrometry, but they detect only the pathogen they are designed for and are therefore only supplementary to traditional methods.[5]

The common public misunderstanding that antibiotics can cure everything from common colds to serious pneumonias no matter the causing agent, may put pressure on clinicians to prescribe antibiotics to any type of infection. This pressure in addition to diagnostic uncertainty, result in large numbers of antibiotic prescriptions to what is most certainly viral infections, quite against guidelines.

METHODS FOR DISCRIMINATION BETWEEN VIRAL AND BACTERIAL INFECTIONS

There are also methods that do not identify the actual pathogen, but that are used to discriminate between viral and bacterial infections. The Complete Blood Count (CBC) that is used to evaluate overall health and detect a wide range of disorders, including anemia and leukemia, is also used to discriminate between viral and bacterial infections by measuring white blood cells. The CBC is performed at hospital laboratories and the result is available, at best, in a couple of hours. In many cases a CBC is unnecessary since the data is often underutilized. In a survey, it was found that only four of the eleven parameters routinely reported in the CBC battery were found always useful by nine out of ten physicians. The authors of the study speculate that data that are not useful to clinicians might actually impede their perception and comprehension of essential data and contribute to errors in medical judgement.[9] A useful alternative to the CBC is a White Blood Cell count (WBC) and hemoglobin in combination. It has been shown that when these two tests give normal values, in nine out of ten cases the CBC is also normal. For the remaining tenth, the CBC profile had only minor deviations from the reference ranges that were of minor clinical significance. WBC and hemoglobin can be analyzed point-of-care, and consequently, this offers a simpler and more effective way of predicting normality of the CBC.[10]

MORE EVIDENCE-BASED CLINICAL DECISIONS WITH ACCESS TO RAPID TEST RESULTS

There are a couple of other methods used to discriminate between bacterial and viral infections. One is the C-reactive protein (CRP). It is an acute-phase protein measured in plasma, whose levels rise in inflammation. Normal concentration in healthy human serum is between 5 and 10 mg/L. It rises in response to infection, more in bacterial (40–200 mg/L), than in viral infection (10–40 mg/L). Another method is the WBC count. A low or normal WBC count is usually associated with viral illness, whereas values >1500/mm^3 are associated with bacterial infection.

Methods for both CRP and WBC are available at the point-of-care. Two test systems (Afinion AS 100CRP POC and HemoCue WBC) were compared to, and found to show good agreement with reference methods performed at hospital laboratories. Both were found accurate enough for the purpose of identifying children at risk of severe bacterial infection.[11,12]

Even though the median levels of both CRP and total WBC are higher in viral infections, the dispersal can be large. In addition, there is often a discrepancy between these two parameters that react differently in different infections as well as depending on the stage of the infection.[13] It has been found that in a substantial portion of children with severe bacterial-type disease only one of the parameters is increased. A way to increase the value of testing for clinical descision making is therefore to combine these two tests. Elevation of both values signifies a high risk of bacterial disease.[14]

Even better predictors of bacteremia than CRP or total WBC are lymphocytopenia and the neutrophil to lymphocyte ratio.[15] Recently, a point-of-care analyzer for WBC and differentiation has become available (HemoCue WBC DIFF). In a study the reliability of this analyzer was compared with a standard reference method (Sysmex XE-5000) regarding accuracy and precision of measuring total WBC and 5-parts differential counts in capillary pediatric samples. It was concluded that the HemoCue WBC DIFF is a reliable method that correlates well with the automated cell counter. Moreover, the authors state that it is eminently suitable in a point-of-care setting, facilitating adequate decision making which could lead to improved clinical outcomes.[16] In another study, the HemoCue WBC DIFF was found to give excellent correlation to three different cell counters (Siemens ADVIA 2120, Beckman Coulter LH750 and Sysmex XS-1000i). The authors conclude that rapid and easy access to test results will assist physicians in making direct and more evidence-based decisions in a number of clinical situations.[17]

Laboratory analyses can tell the difference between viral and bacterial infections. The complete blood count (CBC) performed at hospital laboratories gives accurate and reliable results. The disadvantage hampering quick clinical decisions is that it takes several hours to perform. In addition it produces many parameters that are redundant if the clinical question is only type of infection. Other quicker infection markers are C-reactive protein (CRP), white blood cell counts (WBC) and WBC with differentiation. Some of these parameters can be combined for a more reliable result.

POINT-OF-CARE METHODS CAN CURB INAPPROPRIATE ANTIBIOTIC USE

Adults and children with upper respiratory tract infections are common patients in primary care. As many as 50% or even more, are prescribed antibiotics for this condition, and this represents a high rate of inappropriate use.[18,19,20] Several studies have shown that when physicians have access to reliable point-of-care methods to discriminate between bacterial and viral infections, more accurate prescription of antibiotics is possible.

In a study conducted over a three-year period on more than 700 children with upper respiratory tract infections and non-specific febrile illness, WBC counts dramatically decreased the amount of antibiotics prescribed. Approximately half of the children had symptoms that would typically make the physician inclined to prescribe antibiotics. In this group 96 % of the children had a WBC count < 15 000/mm^3, and thus did not need antibiotics. The remaining four percent needed and were prescribed antibiotics. With this approach, return visits were infrequent during the two-week period that followed and no child with a significant bacterial infection was missed.[21]

In another study two WBC count devices used to assist in antibiotic treatment decisions were compared. The Cell-Dyn 1800 counter and the HemoCue WBC were found to produce comparable results in 120 children with acute illness in pediatric practice. Moreover, performing a WBC count as part of diagnosing resulted in a 73 % decrease in antibiotic prescriptions. Among the children that were not prescribed antibiotics, only 3 % returned for a second visit related to their first office visit. The authors point out that the HemoCue WBC device has the advantages of requiring only one drop of capillary blood and one minute to produce a result, but has the disadvantage that it only produces a total WBC count whereas the Cell-Dyn provides a complete blood count and automated WBC differentials.[22]

These results are corroborated in an Italian study on 792 children aged between 2 and 14 years with symptoms of non-specific upper respiratory tract infection including a fever.[23] The children were randomized into two groups: the Leukocyte group were a WBC count was performed point-of-care (HemoCue WBC) as part of the clinical investigation, and a Control group that were treated with antibiotics according to the Delayed antibiotics prescription strategy.

In the Leukocyte group, children with a WBC count <15000/mm^3 were symptomatically treated. For children with a WBC count >15000/mm^3 the pediatrician was given the choice whether or not to prescribe antibiotics. All children were followed up after 48 hours. In the Leukocyte group, children who were still febrile or were feeling worse were then given antibiotics. On the final doctor's office visit at seven days for both groups, recovery, complications and any side-effects of antibiotic treatment were recorded. The results showed that 88 % of the children in the Leukocyte group with a WBC count <15000/mm^3 at the first visit had become afebrile in 48 hours. 12 % still had a fever and these children (except one) received antibiotic treatment. On the seven-day follow-up, 86 % of the patients were considered recovered. According to the authors, it is remarkable that 37 of the 44 patients receiving antibiotics at the 48-hour follow-up were not considered recovered.

In the Leukocyte group, 56 children had a WBC count >15000/mm^3. They were considered at high risk of having a bacterial infection and were prescribed antibiotics. At 48 hours 89 % had become afebrile and after seven days 73 % hade recovered. In total 23 % of the patients in the Leukocyte group were treated with antibiotics. In the Control group, all patients were given antibiotics according to the delayed antibiotics prescription strategy. At the 48-hour follow-up 93 % had become afebrile, and after seven days 73 % had recovered.

In conclusion, with the help of the point-of-care WBC count, a 77 % reduction of antibiotics prescription was observed compared to the Control group. There was no difference in recovery or in the number of patients becoming afebrile between the Leukocyte group and the Control group. By adding a point-of-care WBC count to the ordinary clinical investigation together with a 48-hour follow-up by phone or office revisit, prescriptions of antibiotics could substantially be reduced without any significant difference in terms of recovery, complications or hospitalization.

There is still a substantial overuse of antibiotics in medical practice. The authors of this study present a standardized method to be used at doctor's offices. A 77 % reduction of the prescription rate of antibiotics to one of the most common reason to seek medical help in primary care; upper respiratory tract infections, compared to the existing practice would lead to a potential decrease in antimicrobial resistance and also to a reduction in pharmaceutical spending.

Several studies have shown that use of antibiotics can be limited with quite simple means and without negative effects on patients' health. In lack of accurate point-of-care methods for infection markers, the "Delayed antibiotics prescription strategy" can be adopted. The decision to start antibiotics or not is then actually up to the patient. With reliable point-of-care methods at hand, the decision is instead in the hand of the clinician and as much as three quarters of the otherwise expected prescriptions of antibiotics can be prevented. When analysing infection markers point-of-care becomes routine in the world's primary care clinics, we stand a good chance of limiting further development of antibiotic resistance.

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