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Emerging Antibiotic Resistance of Blood Stream Infections among Children

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Abstract

Antibiotic resistance is a serious problem in the management of childhood infections. Bacteria have developed various mechanisms of resistance. Indiscriminate and irrational use of antibiotics have led to the emergence of superbugs which have developed resistance to multiple antibiotics. Nowadays research are showing promising role of usage of older antibiotics for treatment of resistant infections. Multidrug resistant gram negative infections is a challenging situation where combination therapy and drugs with gram positive coverage like vancomycin are showing positive results. Ampicillin is losing sensitivity and protocols have been modified in using cephalosporins as the first line in some units. Carbapenam resistance and ESBL are emerging among hospitalised patients. Similarly emergence of community acquired MRSA possessing a new virulence toxin (Panton-Valentine leukocidin) is a serious threat among childhood infections. Unfortunately of late only minimal resources are directed to the development of newer antibiotics. Its time to consider the emerging antibiotic resistance particularly among children as a serious issue and start rational antibiotic practice and develop unit specific antibiotic policy to fight against antibiotic resistance.

Keywords:

Introduction

The emergence, growth and spread of bacteria with increasing antibiotic resistance is a signi icant health risk to children. Although antibiotics can be life-saving, its overuse leads to the development of resistance. Bacteria have developed varied mechanisms of resistance to all classes of antibiotics like (1) inactivation of the antimicrobial, (2) alteration of the site of antibiotic activity and (3) isolation of the target site from the antibiotic [1]. Mechanisms of resistance to antimicrobials used to treat infectious disease have been known since before antibiotics were introduced into routine clinical usage [2].

Objective

To review the emerging antibiotic resistance of blood stream infections among children.

Methodology

We conducted a systematic search on Pub-Med and Google scholar; reports from WHO and other organizations. We have used search terms as antibiotic resistance children.

Burden of antibiotic resistance in children

Prescribing Support Unit (PSU) showed that out of the 40 million antibacterial prescriptions per year in primary care, around 12 million were for children. Children have high rates of minor infection but because of their increased susceptibility to serious bacterial infection are frequently prescribed for antibiotics [3]. About 55% of children aged 0-5 years in the UK receive an average of 2.2 prescriptions for a β lactam antibiotic each year [4]. Prescribing amoxicillin to a child more than triples the mean MIC (9.2 μg/ml vs 2.7 μg/ml, p=0.005) [5]. The correlation between community use of penicillin and penicillin resistance across 19 European countries has been reported as 0.84 [6]. Co-trimoxazole resistant pneumococci was recovered in 52% of children one week after malaria treatment with co-trimoxazole compared with 34% in controls [7].

Economic burden due to antibiotic resistance

According to a recent study in Thailand, in 2010, antimicrobial resistance was responsible for at least 3.2 million extra hospitalization days and 38,481 deaths, and for losses amounting to US$ 84.6-202.8 million in direct medical costs and more than US$ 1,333 million in indirect costs [8].

Antibiotic usage and development of resistance

A meta-analysis of four studies has shown that antibiotic treatment for a urinary tract infection results in a 2.5 times greater risk that a subsequent urinary tract infection in the next three months is due to an antibiotic resistant *E. coli*. Similarly, antibiotic treatment results in an overall 2.4 times greater risk that a respiratory tract infection in the subsequent 12 months is due to an antibiotic resistant *S. pneumoniae*, *Haemophilus influenzae* or *S. pyogenes*. Antibiotic treatment results in a 3 times greater risk that any staphylococcal disease in the next three months is due to MRSA [9].

Gram negative infections

Because of the rapid spread of antimicrobial resistance and slow development of novel antimicrobials, treatment of Gram-negative infections treatments is challenging. In the last decade, polymyxins B and E (colistin) have been used to treat infections due to multidrug resistant Gram-negative bacteria [10]. Colistin-resistant clinical isolates have been reported more recently [11]. Old antibiotic agents,

such as fosfomycin, are now being considered potential treatment alternatives due to the lack of new antibiotics [12]. Experimental evidences are emerging that even drugs active only against Gram-positive microorganisms, such as vancomycin, may have activity against Gram-negative bacteria when combined with other antibiotics [11]. Colistin and rifampicin combination [13] and combination of colistin with vancomycin [14] have been suggested for treatment of MDR *A. baumannii* .

Ampicillin resistance

Of late, there is emerging resistance to first line antibiotics like ampicillin. None of the *E.coli* isolated were susceptible to ampicillin in some studies [15,16]. In response to increasing rates of ampicillin resistance in the 1990s, some units in high-income countries have changed empirical sepsis treatment policy to include a cephalosporin (with or without ampicillin or an aminoglycoside) [17,18].

Extended spectrum betalactamase (ESBL)

ESBLs are plasmid mediated in association with other antibiotics. The prevalence of ESBL have increased from 0.47% to 1.7% [19] and 2.6% to 3.8% [20] in various studies. *E. cloacae* was the most ESBL producer followed by *K. pneumoniae* and *E. coli* [21]. Resistance of *A. baumannii* to carbapenems is almost due to production of metallo-β-lactamases and lost D2 porines.

Emerging carbapenem resistant *Kleibseilla pneumoniae*

Carbapenem-resistant *Klebsiella pneumoniae* (CR-KP) produce enzymes that degrade carbapenems, a treatment of last resort for other infections. CR-KP infections are commonly treated with tigecycline and colistimethate, with an estimated 70% response rate [22]. In some hospitals in the northeastern US, *Klebsiella* resistance to ceftazidime has risen to over 50% [23]. Resistance to polymyxin B and resistance to imipenem were found in 100% and 91% of *K. pneumoniae* isolates [24]. Only 20-30% *Klebsiella* are Gentamicin sensitive [25,26].

E.coli: Resistance of *E. coli* to penicillin was first described in 1940 and the transfer of genetic material coding for resistance was described in 1952 [27]. The rate of penicillin resistance has increased by more than 300% and cefotaxime resistance increased by more than 1000% over a recent 5-year period [28].

P. aerugonisa: In a recent study all *P. aeruginosa* isolates were resistant to meropenem, but susceptible to colistin; the genes blaSPM and blaKPC were found in 82% and 25% of them, respectively; synergistic effect was seen only in combinations of colistin with meropenem (43%), meropenem with amikacin (36%) and colistin with amikacin (7%) [24].

S. aureus: Penicillin resistant *Staphylococcus aureus* confronted London civilian hospitals very soon after the introduction of penicillin in the 1940s [29]. The proportion of *S. aureus* resistant to methicillin have increased from below 5% in 1982 to 34% in 1994 [30]. In 2001 in the US and the UK, 40-60% of nosocomial *S. aureus* strains were methicillin-resistant (MRSA) and usually MDR [31]. Today, MRSA strains differ from the hospital strains and possess a new virulence toxin (Panton-Valentine leukocidin) [32]. The so called 'community-acquired MRSA' is resistant to almost all Beta-lactam antibiotics.

Streptococcus pneumonia: The WHO estimates that from 800000 to one million children die every year due to invasive pneumococcal disease and more than 90% of the deaths occur in developing countries [33]. Penicillin-resistant *S. pneumoniae* (PRSP) was first isolated clinically in Australia in 1967 [34]. Chromosomal gene changes can alter the structure of penicillin-binding proteins of *S. pneumoniae*, thereby decreasing the binding affinity for penicillin and cephalosporins resulting in resistance [35]. Resistance of *S. pneumoniae* to penicillin and cephalosporins is not mediated by b-lactamase enzymes. Hence treatment with b-lactamase-resistant drugs, such as extended spectrum cephalosporins or combinations of broad spectrum penicillins plus clavulanate or sulbactam, offers no advantage. Resistance to penicillin has increased from 6% in 1992 to 42% in 2000; Erythromycin resistance has increased from 1% in 1992 to 44% in 2000; Resistance to trimethoprim-sulfamethoxazole has increased to 48% [36]. The incidence of cefotaxime and ceftriaxone-nonsusceptible *S. pneumoniae* isolates has increased to 20% over the last 5 years [37]. Resistance to penicillin and ceftriaxone was detected in 23.6% and 12.5% of the pneumococcal strains, respectively, and predominated in children aged two years or less and during the 2005-2009 period [38]. The percentage of respiratory tract isolates resistant to erythromycin, penicillin, levofloxacin and telithromycin were 29.3%, 21.2%, 0.9%, and 0.02%, respectively [39].

Enterococci: *Enterococci* have emerged as important nosocomial pathogens [40] ranking only second to staphylococci, accounting for ~12% of hospital associated infections yearly in the US [41]. *Enterococci* show intrinsic low resistance to a large number of antibiotics (β-lactams, lincosamines, aminoglycosides and trimetoprim-sulfamethoxazole) [42]. Unlike other bacteria like *staphylococci*, the production of β-lactamases in *Enterococci* is not inducible, but constitutive. *E. faecalis* is between 10 to 100 times less sensitive to penicillin than streptococci, whereas *E. faecium* is at least 4 to 16 times less susceptible than *E. faecalis* [43]. *E. faecium* also has LD-transpeptidase mediated resistance which is insensitive to β-lactams [44]. Vancomycin resistance has increased from 7.9% in 1993 to 23% in 1998 [45]. Prevalences of VRE colonization ranges from 30% to 50% in general medical and surgical inpatients [46].

Conclusion

Unlike 1980s, when large number of new antimicrobials were developed on a regular basis, nowadays minimal resources are devoted to development of newer antimicrobials. In the era of 'Superbugs' which are resistant to several different **antibiotics**, rational antibiotic policy and optimizing the use of older antibiotics are imperative to prevent the emergence of antibiotic resistance.

Conflict of Interest

The authors have no conflicts of interest that are directly relevant of the content of this manuscript.

Authors contribution

All authors made substantial contributions to the acquisition of data. All authors read and approved the manuscript prior to publication.

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