Is Chloramphenicol Making a Comeback?

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ABSTRACT:
Background: Due to increasing antimicrobial resistance there has been renewed interest in old drugs that have fallen into disuse because of toxic side effects.
Objectives: To evaluate the susceptibility profile, in our hospital, of Enterobacteriaceae and *Streptococcus pneumoniae* isolates to chloramphenicol and to compare them with the susceptibility to amoxicillin-clavulanate.
Methods: All isolates of Enterobacteriaceae and *S. pneumoniae* recovered in our lab during a one year period were tested for susceptibility to chloramphenicol and amoxicillin-clavulanate or penicillin, respectively.
Results: Of 413 Enterobacteriaceae isolates, 182 (44.1%) were resistant to amoxicillin-clavulanate, but only 76 (18.4%) were resistant to chloramphenicol. Of 189 isolates of *S. pneumoniae*, 4 (2.1%) were highly resistant to penicillin and 73 (38.8%) were partially resistant, while only 2 (1.1%) were resistant to chloramphenicol. None of the 24 *S. pneumoniae* isolates causing invasive diseases exhibited resistance to chloramphenicol
Conclusions: In an era of increasing resistance to many antibiotic preparations, chloramphenicol might have a role in the treatment of intraabdominal and respiratory tract infections.
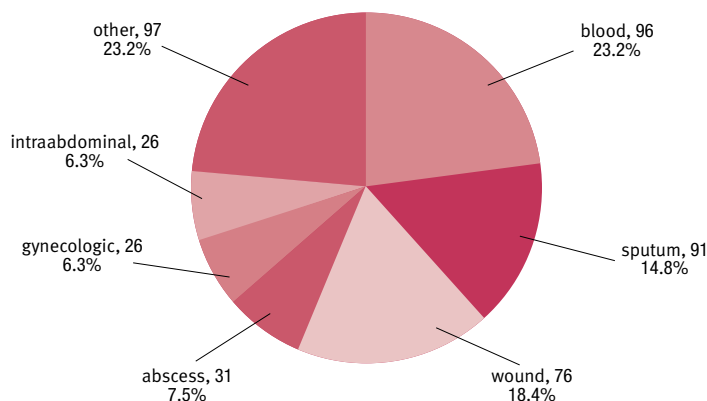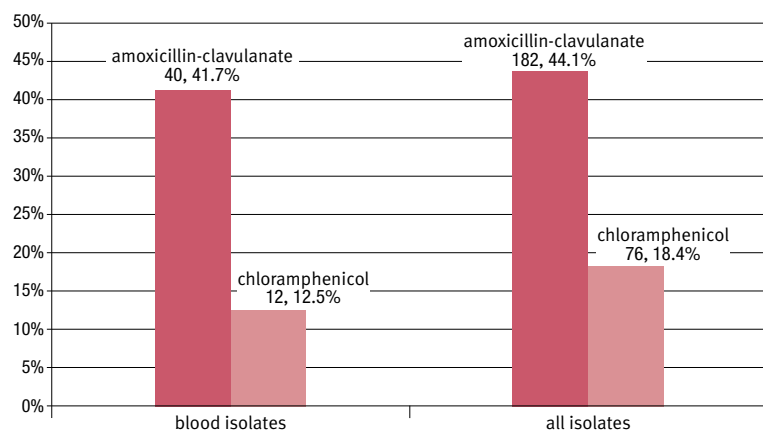
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During the last decade the emergence of highly resistant pathogens has aroused renewed interest in old drugs that have fallen into disuse because of toxic side effects. One such agent is chloramphenicol, which was released for use in the United States in 1949, but due to reports linking its use with the development of aplastic anemia it has long been put aside and is not used as standard therapy in the developed world, though it is still considered first-line treatment for enteric fever and other infections in developing countries. Two types of bone marrow toxicity are associated with chloramphenicol: a reversible dose-related bone marrow suppression, and a rare idiosyncratic reaction of aplastic anemia that has an incidence of 1:24,500-40,800 [1].

Chloramphenicol, a potent inhibitor of protein synthesis, is extremely active against a variety of organisms including bacteria, spirochetes, rickettsiae, chlamydiae, and mycoplasmas. It has bacteriostatic activity against most pathogens but is bactericidal for *Haemophilus influenzae, Streptococcus pneumoniae*, and *Neisseria meningitidis* [2]. Resistance to chloramphenicol has been documented to occur through several mechanisms: reduced permeability or uptake, ribosomal mutation, and acetylation to an inactive derivative [3]. Most reports of resistance were in cases of *Salmonella typhi* [4], while anaerobic bacteria, including *Bacteroides fragilis*, retained 100% susceptibility [5]. Respiratory pathogens such as *H. influenzae* and *S. pneumoniae* have also retained high susceptibility rates, with 99.2% and 99.4% of *H. influenzae* isolates in Canada and the United States respectively, and 91% susceptibility of *S. pneumoniae* isolates [6-8]. The high susceptibility rates noted for chloramphenicol might be due to the very limited use of this drug for many years in the developed world.

Amoxicillin-clavulanate, which has an antimicrobial spectrum similar to that of chloramphenicol, is considered the treatment of choice for many respiratory tract infections including bacterial sinusitis [7], acute otitis media that is severe or has failed to respond to amoxicillin [8], exacerbation of chronic bronchitis, and aspiration pneumonia [9]. It is also considered first-line therapy for other infections including diverticulitis and diabetic foot infections [10]. It is one of the most widely used antimicrobial agents today, especially in the community setting. In Spain during the years 1997–2006 its use increased by 63.6%, while there was a decrease in amoxicillin use [11]. Resistance of pathogens to this agent has also been emerging, with 12% resistance in community-acquired infections and 26.8% of nosocomial pathogens that caused urinary tract infections in London in 2006 [12]. Another emerging problem is the rising incidence of penicillin non-sensitive and multidrug-resistant *S. pneumoniae* isolates.

Due to increasing antimicrobial resistance, we sought to evaluate the susceptibility of gram-negative Enterobacteriaceae and *S. pneumoniae* to chloramphenicol in our hospital and to compare it with the susceptibility to amoxicillin-clavulanate in order to decide whether the time has come to put chloramphenicol back into the arsenal of antimicrobial agents for the treatment of respiratory tract and intraabdominal infections.

Figure 1. Isolates of Enterobacteriaceae by source (n=413)

Figure 2. Resistance of Enterobacteriaceae to chloramphenicol and amoxicillin-clavulanate (as % of all isolates) (n=413)

Table 1. Resistance of Enterobacteriaceae by species to chloramphenicol and amoxicillin-clavulanate

Bacteria	n	Resistant to chloramphenicol	Resistant to AC	P value
E. coli	166	24 (14.5%)	46 (27.7%)	‹ 0.01
Klebsiella spp.	83	18 (21.7%)	23 (27.7%)	0.01
Enterobacter spp.	55	11 (20.0%)	51 (92.7%)	‹ 0.01
Proteus spp.	41	14 (34.2%)	18 (43.9%)	0.68
Citrobacter spp.	29	0 (0%)	5 (13.3%)	0.06
Serratia spp.	18	3 (16.7%)	18 (100%)	‹ 0.01
Morganella spp.	14	5 (35.7%)	13 (92.9%)	‹ 0.01

Susceptibility tests for amoxicillin-clavulanate and chloramphenicol were performed with the Kirby Bauer disk-diffusion test and interpreted according to the Clinical Laboratory Standards Institute (CLSI) Performance Standards for Antimicrobial Susceptibility Testing guidelines [13].

Statistical analysis was done using the SPSS system. Statistical significance was considered $P < 0.05$

RESULTS

During the one year period 1 September 2007 to 31 August 2008, a total of 413 isolates of Enterobacteriaceae were cultured in our lab, including community and nosocomial isolates. As shown in Figure 1, 96 (23.2%) were isolated from blood cultures, 76 (18.4%) from wound cultures, 61 (14.8%) from sputum, 26 (6.3%) from intraabdominal infections, 26 (6.3%) from gynecologic and obstetric infections, 31 (7.5%) from abscesses, and 97 (23.5%) from other sites.

Escherichia coli was the most frequent isolate (166, 40.2% of all), followed by *Klebsiella* spp. (83, 20.1%) and *Enterobacter* spp. (55, 13.3%). Of all Enterobacteriaceae isolates, 182 (44.1%) were found to be resistant to amoxicillin-clavulanate, but only 76 (18.4%) to chloramphenicol ($P < 0.01$).

When looking at blood isolates, we noted a significant difference between susceptibility to these two agents, with 40 (41.7%) resistant to amoxicillin-clavulanate vs. 12 (12.5%) to chloramphenicol ($P < 0.01$) [Figure 2]. As shown in Table 1, a higher resistance rate to amoxicillin-clavulanate vs. chloramphenicol was found among all Enterobacteriaceae, with statistically significant differences found in *E. coli, Klebsiella* spp*., Enterobacter* spp*., Citrobacter* spp*., Serratia spp. and Morganella* spp. The species that were most resistant to amoxicillin-clavulanate were *Serratia* (100% resistance), *Enterobacter* (92.7%) and *Morganella* (92.9%).

During the study period we tested 189 isolates of *S. pneumoniae* for susceptibility to penicillin G and 177 isolates for susceptibility to chloramphenicol (for *S. pneumoniae*, susceptibility to amoxicillin-clavulanate is considered equivalent to that of penicillin G and is not routinely tested). The suscepti-

MATERIALS AND METHODS

All isolates of Enterobacteriaceae recovered in the microbiology laboratory of HaEmek Medical Center during a one year period (1 September 2007 to 31 August 2008), excluding those from urine and feces, were tested for sensitivity to chloramphenicol and amoxicillin-clavulanate. All isolates of *S. pneumoniae*, from all sites, recovered in our microbiology lab between 1 September 2007 and 31 April 2008 were tested for sensitivity to penicillin and chloramphenicol.

Identification of Enterobacteriaceae spp. was performed manually via their metabolic profile using routine conventional bacteriologic phenotypic manual methods or alternatively using a VITEK II instrument employing a gram-negative "card" (Bio-Merieux, Marcy-L'etoile, France. *S. pneumoniae* was identified according to α-hemolytic appearance, a positive optochin test, and agglutination with Phadebact Pneumococcus (BACTUS AB, Lunastigen, Huddinge, Sweden).

Figure 3. Resistance of isolates of *S. pneumoniae* to chloramphenicol (n=177) and penicillin (n=189) as % of all isolates tested
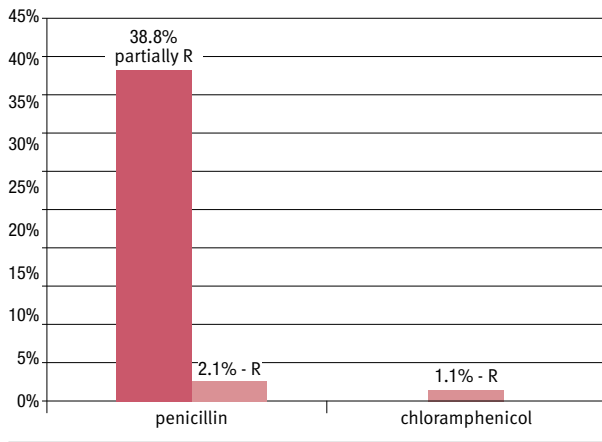
bility profile of these isolates showed a clear and statistically significant advantage for chloramphenicol over penicillin G, with 2.1% of isolates highly resistant to penicillin, 38.8% with intermediate resistance to penicillin, and only 1.1% resistant to chloramphenicol (*P* < 0.01) [Figure 3].

Of the four isolates that were highly resistant to penicillin, three remained susceptible to chloramphenicol. Of the 24 isolates causing invasive diseases (mostly blood and cerebrospinal fluid isolates), none exhibited resistance to chloramphenicol, and 6 isolates (25%) were intermediately resistant to penicillin.

DISCUSSION

Due to increasing resistance of many bacteria to a wide variety of antimicrobial agents, we sought to investigate the sensitivity profile of bacterial isolates at our hospital to chloramphenicol in order to see if this long forgotten antibiotic can be put back into our armamentarium of treatments for intraabdominal and respiratory tract infections, especially in cases of multidrug-resistant pathogens. In particular, we wanted to compare the resistance rate of Enterobacteriaceae and *S. pneumoniae* to chloramphenicol and amoxicillin-clavulanate, since both antibiotics have a similar antimicrobial profile and can be used for similar clinical indications.

We found a significant advantage for chloramphenicol over amoxicillin-clavulanate among 413 isolates of Enterobacteriaceae cultured at our hospital during a 12 month period, excluding urinary isolates, where susceptibility to chloramphenicol was not assessed because it is minimally excreted in urine and thus not considered a good treatment option for urinary tract infections. Resistance to chloramphenicol was 18.4%, as compared to 44.1% resistance to amoxicillin-clavulanate (odds ratio 2.4), with the advantage of chloramphenicol being even more conspicuous in blood isolates (12.7% vs. 41.7% resistance, odds ratio 3.3).

The lower resistance rate to chloramphenicol was observed in all the members of the Enterobacteriaceae, reaching statistical significance in *E. coli, Klebsiella* spp*., Enterobacter* spp*., Citrobacter* spp*., Serratia* spp. and *Morganella* spp. The species that were found to be most resistant to amoxicillin-clavulanate were *Serratia* (100% resistance), *Enterobacter* (7.3%) and *Morganella* (7.1%). These species are all known to harbor the *AmpC* gene, which confers acquired resistance to beta lactams under antibiotic pressure.

Increasing resistance to amoxicillin-clavulanate among Enterobacteriaceae has been reported by many other authors. In London in 2006, 12% were community acquired and 26.8% were nosocomial pathogens causing urinary tract infections resistant to amoxicillin-clavulanate [12]. Emerging resistance to amoxicillin-clavulanate has also been reported from Spain, where isolates of *E. coli* from 42 hospitals around the country during the period 2003–2006 showed an increase in non-susceptibility to amoxicillin-clavulanate from 9.3% to 15.4%, paralleling an increase to 34.7% in amoxicillin-clavulanate use in those years [14].

An even more striking finding in our study was the low resistance rate of *S. pneumoniae* to chloramphenicol, with 1.1% resistance to this antibiotic in all isolates and none in invasive isolates. The susceptibility of *S. pneumoniae* to chloramphenicol was compared to that of penicillin, the latter being an appropriate surrogate drug for *S. pneumoniae* susceptibility to amoxicillin-clavulanate, which is not routinely tested. Among *S. pneumoniae* isolates, 40.9% were non-susceptible to penicillin (2.1% demonstrating high level resistance and 38.8% intermediate resistance) vs. only 1.1% to chloramphenicol (*P* < 0.01).

Over the past two decades antimicrobial resistance among *S. pneumoniae* isolates has also escalated dramatically worldwide. Currently, 20–30% of *S. pneumoniae* isolates worldwide are defined as multidrug resistant (resistant to three or more different classes of antibiotics) [15]. Only 39.2% of 113 isolates of *S. pneumoniae* from Spain during 2005–2006 were penicillin susceptible, 31.6% were partially resistant and 29.2% highly resistant [16].

Amoxicillin-clavulanate resistance mechanisms include beta-lactamase overproduction, AmpC cephalosporinase hyperproduction, and inhibitor-resistant penicillinases [17]. All these mechanisms might be favored by increased consumption of this antibiotic. In contrast, the use of chloramphenicol has been highly restricted in Israel as well as other western countries, which explains the low resistance rates in our study.

Chloramphenicol was one of the first antimicrobial agents discovered to have a wide antibacterial spectrum. Soon after its use became widespread, reports of bone marrow suppression emerged and in 1967 a report of several hundred cases of chloramphenicol-associated blood dyscrasias was published [18], with the distinction of two different forms: a dose-related reversible hematopoietic suppression and a fatal idiosyncratic

aplastic anemia with an incidence of 1:24,500–40,800 courses of treatment [1]. Most of the reported cases of idiosyncratic aplastic anemia occurred after use of an oral preparation; this was attributed to the absorption of byproducts formed by the interaction between chloramphenicol and enteric bacteria [19]. To date, there have been 12 reports of irreversible aplastic anemia after intravenous chloramphenicol use, and a few reports of cases following the use of eyedrops [20,21]. Other commonly prescribed medications such as the antipyretic dypirone, drugs for the treatment of hyperthyroidism, and other antibiotic preparations have also been reported to cause irreversible bone marrow suppression with an incidence as high as 1:1439 prescriptions for dypirone [22]. The finding of chloramphenicol-induced aplastic anemia almost eradicated its use in the United States and Europe; however, it is still successfully used in developing countries due to its low price and high accessibility.

Reports of susceptibility of bacterial isolates to chloramphenicol during the past decade are mostly from developing countries, demonstrating relatively high resistance rates of Enterobacteriaceae, with a 46% resistance rate of *E. coli* isolates from Ghana [23] and 53% resistance among *Shigella* spp. isolates from Ethiopia [24]. Gram-positive bloodstream isolates from Iran during 2001–2004, on the other hand, demonstrated high susceptibility rates to chloramphenicol (86.4%) [25]. It is likely that among isolates of Enterobacteriaceae and gram-positive bacteria in the developed world, chloramphenicol susceptibility has been retained due to its highly limited use.

CONCLUSIONS

In an era of increasing resistance to many antibiotics, chloramphenicol might have a role in the treatment of intraabdominal infections and respiratory tract infections caused by multidrug-resistant pathogens. In our hospital we increased the use of chloramphenicol, from 462 defined daily doses in 2008 to 585 during the period January–May 2009. Of course, more data on susceptibility rates of bacterial isolates to this drug from developed countries would permit reassessment of the therapeutic use of this drug.

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