PATTERNS OF ANTIMICROBIAL SUSCEPTIBILITY AMONG BACTERIAL PATHOGENS IN SOUTH AFRICA

The choice of empirical antimicrobial therapy should be guided by current data on susceptibility patterns of bacteria obtained from surveillance data.

ANNE VON GOTTBERG

MB BCh, DTM & H, FCPath (SA) Micro

Clinical Microbiologist

Respiratory and Meningeal Pathogens Research Unit (RMPRU)
Medical Research Council/
University of the Witwatersrand/
National Institute for Communicable Diseases
Johannesburg

Anne von Gottberg completed her medical training at the University of the Witwatersrand and then joined the Division of Clinical Microbiology and Infectious Diseases at Wits to specialise in clinical microbiology. At present she works with national surveillance bacterial isolates that cause pneumonia and meningitis, teaches at the University, and attends clinical ward rounds.

Antimicrobials are frequently used for empirical therapy of suspected infections, before comfirming aetiology. The choice of empirical therapy should be guided by current data on susceptibility patterns of bacteria that have been shown to cause defined clinical presentations, e.g. community-acquired pneumonia (CAP) or uncomplicated urinary tract infections. In South Africa it is essential that we conduct our own regular studies of defined clinical syndromes to identify their infectious causes and to evaluate their resistance profiles, as aetiology and susceptibility patterns may vary from country to country. Within South Africa, these data may differ between regions.

There are many public, private and academic centres which collect data. For example, different centres in the country collect a wide range of data about the agents causing sexually transmitted infections (STIs) and their susceptibility to antimicrobials. This guides clinicians in their choice of therapy, without the need to take specimens from each patient for diagnosis or susceptibility testing. The well-described syndromic approach followed in many STI clinics in South Africa, is used in an attenuated form for many other infectious presentations: clinicians make the diagnosis of CAP (the syndrome) and use published, anecdotal or own-experience data to assist them in the management of this infection. Although specimens may be submitted for microbiological evaluation of respiratory tract infections, the yield may be disappointing.[1]

INTERPRETING SURVEILLANCE DATA

The purpose of surveillance is to monitor accurately the spread of resistance, and to limit this by appropriate antimicrobial usage and infection control strategies. In order for this to happen, surveillance data need to be returned timeously to clinicians and the committees that formulate treatment guidelines.[2]

In a study in the USA it was shown that data from a limited number of laboratories, rather than from all laboratories in a state, could reliably detect large changes in penicillin susceptibility in pneumococci. However, this did not accurately reflect an area's actual percentage of penicillin-resistant isolates.[3]

We are clearly seeing a high degree of variability in resistance data from laboratories and groups of laboratories in South Africa. This may be explained by a number of factors that need to be kept in mind when interpreting surveillance data (Table I).

Disc diffusion testing is the most common form of routine susceptibility testing performed in diagnostic clinical laboratories. It may be adequate to guide the use of antibiotics for some bacteria reliably (e.g. Gram-negative bacteria belonging to the family Enterobacteriaceae, e.g. *Escherichia coli*). In other cases the identity of

Table I. **Important components of surveillance systems to be kept in mind when interpreting data**

At laboratory level
Method of susceptibility testing: disc diffusion testing v. MIC determination with E tests or MIC determination with broth or agar dilutions
Antibiotics selected for testing
Quality assurance programmes within the laboratory
Information technology or method of data capture and analysis

Organism source
Human or animal
Clinical or environmental
Unique v. repeat isolates
Defined specimens, or all specimens included
Restricted organisms, or all organisms included

Patient selection
Community v. hospital population
Any clinical inclusion and exclusion criteria

Adapted from Masterten RG. *J Antimicrob Chemother* 2000; **46:** 53-58.[2]

the organism may be sufficient to predict susceptibility to penicillin, e.g. *Streptococcus pyogenes* or *Streptococcus agalactiae*, where resistant isolates have not been described.

With other organisms, such as *Streptococcus pneumoniae*, additional factors need to be kept in mind. Oxacillin discs are used to predict penicillin susceptibility in the laboratory, as this has been found to be more accurate than using penicillin or ampicillin discs. Zone sizes read as resistant on oxacillin disc testing may occur with penicillin-resistant, intermediate or certain susceptible strains, and therefore monitoring of resistance should not be based on disc diffusion testing alone. Clinical reporting may be sufficient with this form of testing, because if the zone sizes are at least equal to 20 mm, as determined in the laboratory, the isolate can reliably be reported as being susceptible to penicillin. Minimum inhibitory concentration (MIC) testing is the gold standard for predicting susceptibility, and can be determined by using E tests (used in clinical diagnostic laboratories) or the reference agar or broth dilution methods (used in academic centres or larger laboratories in South Africa).

Breakpoints define the concentration of the antimicrobial, below which the isolate is called susceptible and above which the isolate is determined as resistant.

In addition to the *in vitro* testing of the organism against the antimicrobial, the site of the infection and the penetration of the drug to the site must be considered when discussing optimal therapy (pharmacokinetic and pharmacodynamic parameters). For example, the breakpoints for determination of susceptibility of pneumococci vary depending on the site of infection. Breakpoints for isolates from patients with meningitis are higher than those for pneumonia, because achievable levels of drugs in the cerebrospinal fluid (CSF) are less than those achieved in the alveolar space.

RECENT DATA FOR SOUTH AFRICAN ISOLATES

Streptococcus pneumoniae

Resistant *S. pneumoniae* are more commonly found in children, in HIV-seropositive individuals[4] and from non-sterile isolates. Surveillance studies should ideally report according to specimen source and patient age, and discuss details of the patient population and their clinical presentations.

Cerebrospinal fluid isolates

Over a period of 12 months (August 2001 - July 2002), 101 of 526 viable isolates (19%) (including 9 from the private sector) from CSF were intermediately resistant to penicillin, and 2 (0.4%) were high-level resistant. These were taken mainly from the public sector. None of these 526 isolates was resistant to cephalosporins on MIC testing (Anne von Gottberg — unpublished data). Recent data from private laboratories in Johannesburg have shown an increase in the number of pneumococci isolated from CSF that are resistant to third-generation cephalosporins: 25% of 14 isolates during a 6-month period from July 2002 to December 2002 (Adrian Brink and the Antibiotic Surveillance Forum, ASF — personal communication).

Empirical therapy of meningitis with ceftriaxone or cefotaxime covers penicillin-resistant isolates. However, the addition of vancomycin is required for adequate therapy for 3rd generation cephalosporin-resistant isolates. Because of the frequency of these resistant isolates in the USA the empirical therapy of meningitis in that country includes vancomycin. This is not currently recommended in South Africa, although we are approaching the time when such therapy may be necessary. Surveillance data are essential to guide such decisions.

Blood culture isolates

Penicillin resistance increased from 4.9% in 1979 to 14.1% in 1990 for normally sterile site isolates from patients presenting to the public sector in South Africa.[5] Currently 18% of invasive isolates submitted to the Respiratory and Meningeal Pathogens Research Unit (RMPRU) are resistant to penicillin (Table II). Small numbers of isolates with high-level resistance to penicillin were documented (4 of 2 127 tested (0.2%)). Approximately

Table II. **Antimicrobial resistance in invasive pneumococcal isolates sent to RMPRU, NICD (August 2001 - July 2002)**

	No. and % of resistant isolates							
	< 5 yrs (*N* = 746)		≥ 5 yrs (*N* =1 095)		Age unknown (*N* = 286, 2 not tested)		Total (*N* = 2 127, 2 not tested)	
Antibiotic	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Penicillin								
Intermediately resistant*	212	28	131	12	48	17	391	18
Fully resistant†	2	0.3	2	0.2	0	0	4	0.2
Trimethoprim/ sulphamethoxazole	433	58	320	29	89	31	842	40
Cefotaxime	0	0	0	0	0	0	0	0

*0.12 mg/l -1 mg/l.
†≥ 2 mg/l.
RMPRU = Respiratory and Meningeal Pathogens Research Unit; NICD = National Institute for Communicable Diseases.

99 of 2 245 (4.4%) were cases reported from the private sector. Penicillin resistance has remained stable over the past 5 years.[6] Of these isolates, 9% were erythromycin resistant.

Data from the private sector for blood culture isolates in patients with probable lower respiratory tract infections show intermediate resistance to 3rd generation cephalosporins, ranging from 0% to 25% between centres, with no high-level resistance being documented in isolates (Adrian Brink and the ASF — personal communication). Erythromycin resistance of these isolates ranges from 22% to 30%.

Sputum isolates

The role of sputum isolates in diagnosing the aetiology of lower respiratory tract infections is controversial.[1] Pneumococcal isolation may not always represent the true bacterial causation of pneumonia, and unless some effort is made to exclude colonisation, these data may represent only information about colonising pneumococci in a certain population.

Data from a recent study identified high levels of resistance in pneumococci isolated from non-sterile site specimens: 30% intermediate and 46% high-level resistance to penicillin.[7] However, 82% of these isolates were submitted from one laboratory in Pretoria. Additional information about patient characteristics and type of specimen collected would make these very important figures more helpful to clinicians, not only in Pretoria but also in South Africa as a whole.

The Alexander Project received 83 pneumococcal isolates from South Africa in 1996 and 66 in 1997. Intermediate resistance to penicillin was quoted as 31% and 26% respectively, and high-level resistance as 4% and 4.5%.[8] These isolates were from a referral laboratory, which may have led to the biased results.

There is wide variation in susceptibility data for pneumococcal isolates from non-sterile sites. This may be due to a number of factors and additional studies are needed to determine rates of resistance accurately.

Haemophilus influenzae

The proportion of sterile site isolates of *Haemophilus influenzae* producing beta-lactamase and submitted to the surveillance laboratory since 1999 remains constant (Table III).

Beta-lactamase production from *H. influenzae* sputum isolates is documented at 7% in some South African studies.[7, 8] Although not clearly stated, most of these isolates would be non-typeable *H. influenzae*, as non-typeable strains are more commonly described in lower respiratory tract infections without bacteraemia.

Neisseria meningitidis

Increasing MICs of *Neisseria meningitidis* have been documented in South Africa and elsewhere in the world, although the clinical significance of disease caused by these isolates is unknown. Currently penicillin remains the drug of choice for treatment of invasive disease. Ongoing surveillance remains important.

Salmonella spp.

The Enteric Diseases Reference Unit (EDRU) has received a number of multidrug-resistant *Salmonella* isolates from hospitals in South Africa during the past 2 years. These isolates are predominantly *S. enterica* serovar Typhimurium and *S. enterica* serovar Isangi. Many of the *S. typhimurium* and all the *S. serovar Isangi* strains express an extended spectrum beta-lactamase (ESBL). These isolates comprise approximately 50% and 20% respectively of all isolates received at EDRU (approximately 500 isolates each year). Nalidixic acid resistance in *S. serovar Isangi* has increased from 25% to 70% in isolates received in the past 6 months (K H Keddy — personal communication).

ESBL-producing organisms were classically *Klebsiella* sp., and are often associated with nosocomial infection. The above-mentioned *Salmonella* sp.

Table III. **Beta-lactamase production of submitted *Haemophilus* spp. isolates**

Age	Year 1* N	Year 1* B/L +	Year 1* %	Year 2* N	Year 2* B/L +	Year 2* %	Year 3* N	Year 3* B/L +	Year 3* %
Haemophilus influenzae type b									
< 5 yrs	109	14 of 108 tested	13	49	10	20	39	8 of 36	22
≥ 5 yrs	15	1	7	28	6	21	14	1 of 13	8
Unknown	9	2	22	12	3	25	6	0 of 4	0
	133	17 of 132	13	89	19	21	59	9 of 53	17
Haemophilus spp. not type b									
< 5 yrs	23	6	26	18	3	17	32	4 of 30	13
≥ 5 yrs	12	0	0	21	0	0	9	1 of 8	13
Unknown	6	1	17	5	1	20	4	0 of 3	0
	41	7	17	44	4	9	45	5 of 41	12

B/L = Beta-lactamase-producing isolate.
*Year 1: July 1999 - July 2000; year 2: August 2000 - July 2001; year 3: July 2001 - August 2002.

isolates (isolated from blood cultures and stool) may also have been nosocomial infections originally, especially in paediatric wards. Recently patients from the community, without any history of previous hospital admissions, have been presenting to both paediatric and adult wards with these resistant organisms.

Fluoroquinolone-susceptible strains of *Salmonella* that test resistant to nalidixic acid may be associated with clinical failure or a delay in response to therapy in fluoroquinolone-treated patients with extra-intestinal salmonellosis. This may need to be considered when treating patients with bacteraemia due to the Salmonellae mentioned above.

Vibrio cholerae

The current cholera epidemic is associated with a multidrug-resistant strain of *Vibrio cholerae* El Tor Ogawa and *V. cholerae* El Tor Inaba. The current strains are resistant to ampicillin, trimethoprim-sulphamethoxazole, tetracycline (doxycycline) and erythromycin. MICs for nalidixic acid are increasing and recent isolates received at the EDRU show intermediate resistance to nalidixic acid (K H Keddy — personal communication). Rehydration of the patient remains the mainstay of therapy.

CONCLUSIONS

Accurate surveillance of antimicrobial susceptibility, taking into account local needs, is important for the development of rational empirical therapy guidelines.

Some of the data detailed above begin to answer these needs. However, surveillance programmes locally and nationally need to continue to improve their efforts to assist the fight against resistance. Increasing the number of laboratories participating in surveillance systems may improve the accuracy of information.

In order for South Africa to answer this need, both private and public microbiology laboratories have come together to form a surveillance group (National Antimicrobial Surveillance Forum (NASF) — funded by support from pharmaceutical companies*) that will collect data from as many laboratories as possible, and then present these data regularly, with breakdown relevant to clinicians in the private and public sector.

Hopefully this initiative will lead to improved patterns of antimicrobial usage within South Africa.

* Pharmaceutical companies supporting NASF: Abbott, Aspen, AstraZeneca, Aventis, Bayer, Bristol-Myers Squibb, Sandoz (Novartis), GlaxoSmithKline, Lilly, Merck, Sharpe & Dohme, Pfizer, Roche, and Wyeth.

References available on request.

IN A NUTSHELL

Antimicrobial susceptibility surveillance plays an important role in guiding empirical antimicrobial therapy.

Interpreting such data needs to take into consideration the method of testing in the laboratory, the type of specimen from which the organism was isolated, and the type of patient who was selected.

Between 15% and 20% of *Streptococcus pneumoniae* causing meningitis and bacteraemia in South Africa are intermediately resistant to penicillin (levels are higher in the private sector).

High-level resistance to penicillin or resistance to 3rd generation cephalosporins is still uncommon, especially in the public sector.

Multidrug-resistant *Salmonella* species are being isolated throughout the country.

Accurate antimicrobial susceptibility data for all health care sectors need to be a goal for laboratories throughout the country.