Surveillance of invasive Group A *Streptococci* in Belgium (01/01/2009-31/12/2014)

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Knowledge / Experience / Care

Introduction (1)

- Gram positive pathogen, worldwide
- Superficial infections: URTI, skin infections, pharyngitis
- Invasive infections: septicemia, meningitis, cellulitis, pneumonia, necrotising fasciitis, STSS
- High fatality rate: severe scarlet fever, puerperal sepsis, systemic disease
- Virulence factors:
  - M-protein coded by the *emm*-gene
  - Superantigens: Streptococcal pyrogenic exotoxins (Spe proteins; 11 identified: SpeA, SpeC, SpeG-M), streptococcal mitogenic exotoxin Z (SmeZ), streptococcal superantigen (SSA)
  - In general, isolates of the same *emm*-type share a similar SA profile, but variants may occur (Schmitz et al. 2003)

Introduction (2)

- Increase in invasive GAS worldwide during the 80-ies
- Increase in GAS bacteremia in France between 2000-2009 (Plainvert et al. 2011)
- Increase in invasive GAS in Denmark between 2005-2011 (Lambertsen et al. 2013)
- Decrease in GAS between 2006-2007 in Norway (Meisal et al. 2010)
- *Emm*1 and *emm*3 among the most frequent isolated invasive strains (Luca-Harari et al. 2009, Meisal et al. 2010, Friaes et al. 2012)
- All strains sensitive to penicillin so far
- Macrolide, tetracycline and lincosamide resistant GAS strains gradually spread among certain *emm*-types (Harari-Luca et al. 2008, Mihaila-Amrouche et al. 2004, Chen I et al. 2011)

Role: NRC β-hemolytic *Streptococci* not belonging to Group B

CENTRE DE REFERENCE *STREPTOCOCCUS B-HEMOLYTIQUE* INVASIF NON GROUP B

FORMULAIRE A RENVOYER AVEC L'ÉCHANTILLON AU LABORATOIRE DE RÉFÉRENCE :

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IDENTIFICATION DU LABORATOIRE QUI ENVOIE L'ECHANTILLON

Nom du responsable : ……

Nom du laboratoire : ……

Service : ……

Adresse : ……

Code postal + localité : ……

Tél. : …… Fax : ……

Adresse email: ……

Médecin prescripteur + N° INAMI : ……

……

RENSEIGNEMENTS CONCERNANT LE PATIENT

Nom (initiales/autre code) : ……

Sexe : ❑ H ❑ F ❑ inconnu

Date de naissance (ou âge) : ……

Code postal/Localité : ……

Nationalité : ……

Hospitalisation ❑ oui ❑ non

Issue: ❑ guéri ❑ inconnu

❑ décédé (date) :……

TABLEAU CLINIQUE/DIAGNOSTIC CLINIQUE LORS DE LA PRESENTATION

Es-ce une simple pharyngite : ❑ oui ❑ non

Autre tableau cliniques :

- ❑ Septicémie (source inconnu)
- ❑ Ostéomyélite
- ❑ Infections des plaies non-chirurgicales
- ❑ Infection de la plaie chirurgicale
- ❑ Sepsis puerpérale
- ❑ Méningite
- ❑ Cellulite
- ❑ Pneumonie
- ❑ Mono arthrite
- ❑ Polyarthrite
- ❑ Péritonite
- ❑ Fasciite
- ❑ Otite
- ❑ Autre: ……

CADRE RESERVE AU CENTRE DE REFERENCE

INFORMATIONS CONCERNANT LA SOUCHE

Numéro d'identification :……

Date d'isolement : ……

❑ *S. pyogenes* ❑ *S. dysgalactiae* ❑ *S. equi* ❑ Streptococcus spp

❑ De compartiment normalement stérile :

- ❑ Sang
- ❑ liquide synovial
- ❑ Liquide céphalorachidien
- ❑ Liquide pleural
- ❑ Liquide péritonéal
- ❑ Plaies (aspiration profonde)
- ❑ Tissus (veuillez préciser) :……
- ❑ Autre (veuillez préciser) :……

❑ De compartiment normalement non-stérile :

- ❑ Gorge
- ❑ Peau
- ❑ Oreille
- ❑ Plaies (superficielle)
- ❑ Vagin
- ❑Autre (veuillez préciser)……

❑Inconnu ❑ Autre) :……

ANALYSES DEMANDEES POUR LE CNR

❑ Détermination de la CMI (peniciline, erythomycine, clindamycine) (routine, souches invasives)

❑ Mécanismes de résistance aux macrolides (routine, souches invasives)

❑ Détection de gènes de résistance (erythromycine et tétracycline)

❑ Electrophorèse en champ pulsé (PFGE)

❑ M-génotypage (routine, souches invasives)

❑ Détection de gènes super antigène (*S. pyogenes*)

Motiver votre demande :

……

Veuillez contacter Prof. Dr. H. Goossens ou K. Loens (katherine.loens@uza.be, tel 03 821 36 72) si les résultats des tests sont souhaités immédiatement

Invasive streptococcal strains received at the NRC (2009-2014)

Year	Total nr of invasive strains received	Nr of invasive strains received from labs submitting on a regular basis
2009	219/467	192
2010	220/593	194
2011	213/1597	192
2012	229/307	216
2013	221/250	215
2014	242/286	234

Isolation site of Group A *Streptococci*

Isolation site	%
Blood	74.0
Sterile wounds	6.2
Tissue	4.2
Pleural fluid	2.1
Other sterile sites (CSF, peritoneal fluid, synovial fluid, sterile not specified)	13.5

Clinical picture invasive GAS

	2009	2010	2011	2012	2013	2014
Sepsis (%)	**42.2**	**43.9**	**41.6**	**40.3**	**35.6**	**48.2**
Surg Wound (%)	4.2	3.1	2.0	1.9	1.4	4.9
Cellulitis (%)	**6.0**	**4.1**	**8.1**	**8.8**	**7.3**	**8.6**
Fasciitis (%)	2.6	1.5	1.0	1.9	**5.5**	**6.1**
Arthritis (%)	3.1	2.0	2.0	3.2	**5.5**	**1.6**
Meningitis (%)	1.0	1.0	0	0.9	2.7	1.6
Pneumonia (%)	3.1	3.1	**6.1**	**5.1**	**5.0**	**6.1**
Myositis (%)	0.5	0	0	0.9	0	0.4
Puerperal sepsis (%)	2.6	1.5	0.5	1.9	2.7	1.6
Other (%)	15.9	15.3	22.5	16.3	20.1	19.9
Unknown (%)	18.8	24.5	16.2	18.8	14.2	1.0

Presence of virulence genes/*emm*-type

- SpeB and SpeF were detected in 100% of investigated invasive isolates
- Most *emm*1 strains harbour SpeA, 7 strains also harbour SpeC
- 95% *emm*3 strains harbour SSA, >85% harbour SpeA
- All *emm*6 and the majority of *emm*12 strains harbour SpeC
- 83% of all *emm*87 strains harbour SSA and SpeC

Emm-type related to gender

Year	Gender	Nr	*emm1*	*emm89*	*emm3*	*emm28*	*emm6*	*emm75*	*emm12*
2009	M	92	23	7	14	11	3	2	8
	F	97	19	18	10	2	7	3	6
2010	M	101	20	3	11	10	8	3	12
	F	91	12	12	6	13	10	2	3
2011	M	87	22	6	12	5	8	4	6
	F	105	20	8	12	14	7	1	7
2012	M	101	30	6	12	4	1	9	6
	F	114	15	9	15	8	1	13	6
2013	M	109	33	5	18	6	6	4	7
	F	108	33	14	11	7	7	3	4
2014	M	119	29	11	14	3	9	8	6
	F	115	18	21	4	3	7	8	3
Overall	M	609	157	38	79	39	35	30	45
	F	630	117	82	58	47	39	30	29

Antibiotic resistance in Group A *Streptococci* (2009-2014)

Year	Penicillin (%)	Erythromycin R/I (%)	Clindamycin resistance / inducible resistance (%)	Tetracycline R/I (%)
2009[a]	0	3.2/0	0/1.6	7.1/0
2010[b]	0	2.9/5.7	2.8/1.9	7.6/6.2
2011[c]	0	2.4/0.9	0.9/0.5	4.8/3.8
2012	0	1.7/5.7	1.3/6.1	6.5/4.2
2013*	0	4.8	3.2/1.8	14.5
2014*	0	5.3	1.6/3.4	16.7

Tetracycline resistance related to emm-type: tetM>tetO>tetL, *emm*77>*emm*5>*emm*11>*emm*22>*emm*50>*emm*83>other

[a] available for 187/192 strains, [b] available for 182/194 strains, [c] available for 177/192 strains, * Norm EUCAST

Antibiotic resistance in Group A *Streptococci* (2009-2014) related to *emm*-type

Emm-type	Erythromycin (n)	Erythromycin resistance gene	Tetracycline R/I (n)	Tetracycline resistance gene
*emm*77	18	ermA	18/18	tetO
*emm*11	10	ermB	10/10	UNK
*emm*89	5	ermA	1/5	tetM
*emm*58	3	ermA	3/3	tetM
*emm*6	2	1x ermA 1xermB	2/2	tetM
*emm*8	2	ermA	2/2	UNK
*emm*2	1	Mat+mef	/	NA
*emm*12	1	Mat+mef	/	NA
*emm*44	1	ermB	1/1	tetM
*emm*49	1	UNK	1/1	UNK
*emm*73	1	ermA	1/1	tetM
*emm*94	1	ermA	1/1	tetM

Top 4: *Emm*-types invasive GAS (2009-2014)

Year	Most frequent (%)	2nd (%)	3rd (%)	4th (%)	Total (%)
2009	*emm*1 (21.9)	*emm*89 (13.5)	*emm*3 (13.0)	*emm*12 (7.8)	56.2
2010	*emm*1 (16.4)	*emm*28 (12.3)	*emm*6 (9.2)	*emm*3 (8.7)	46.6
2011	*emm*1 (23.4)	*emm*3 (12.5)	*emm*28 (9.9)	*emm*6 (7.8)	53.6
2012	*emm*1 (20.9)	*emm*3 (12.6)	*emm*75 (10.2)	*emm*89 (7.0)	50.7
2013	*emm*1 (30.2)	*emm*3 (13.5)	*emm*89 (8.8)	*emm*28 (6.5)	59.0
2014	*emm*1 (19.5)	*emm*89 (13.3)	*emm*6 (6.6) *emm*75 (6.6)	*emm*3 (6.2)	52.2

Invasive GAS in children <4 years

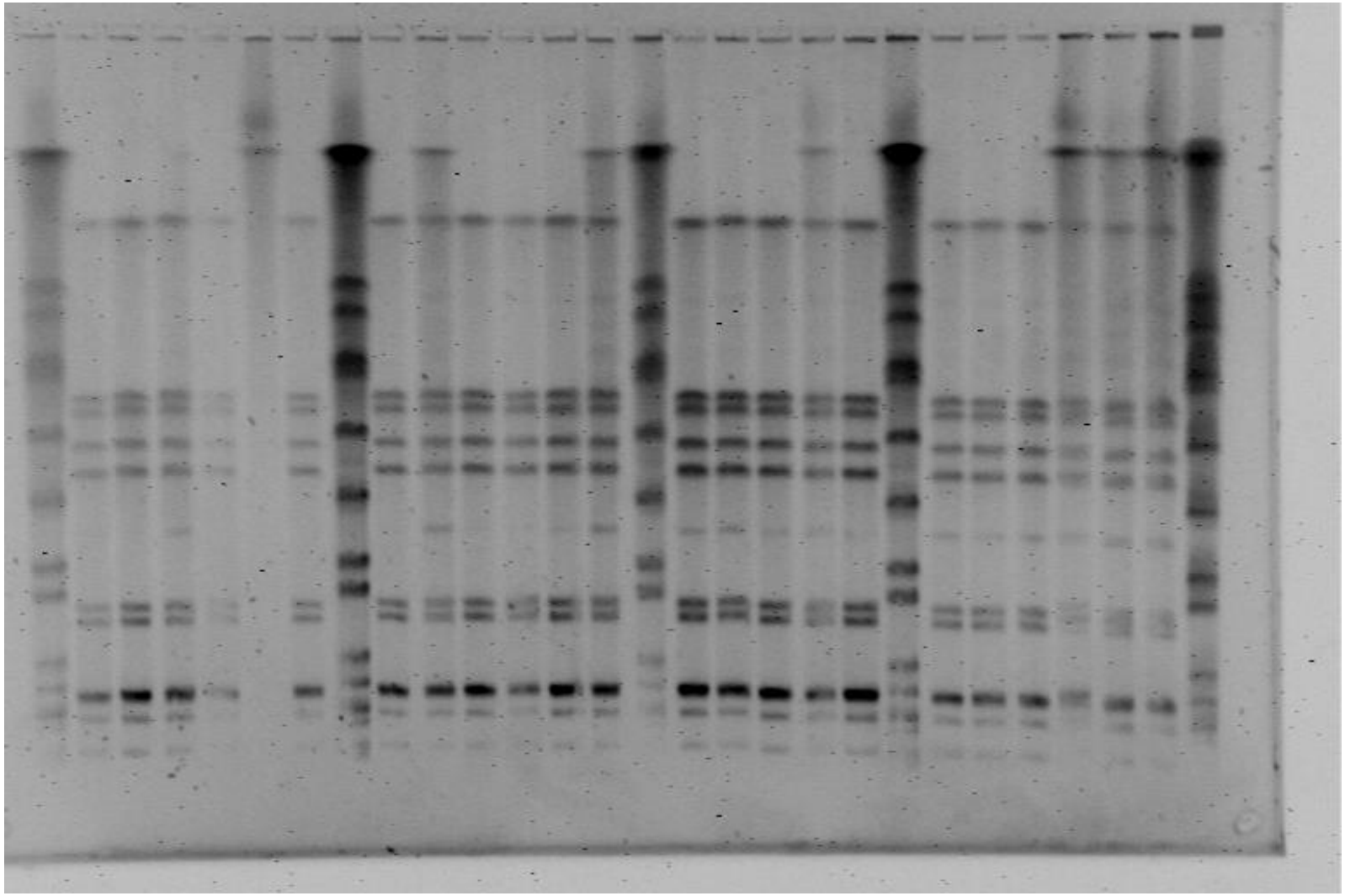
	2009	2010	2011	2012	2013	2014
Invasive strains in children (%)	28/192 (14.6)	27/194 (13.9)	27/192 (14.0)	24/216 (11.1)	37/215 (17.2)	25/234 (10.7)
Emm-type most frequently detected (%)	9/28 (32.1) *emm*12	7/27 (25.9) *emm1*	6/27 (22.2) *emm*12	1/24 (4.2) *emm*1	19/37 (51.3) *emm*1	8/25 (32.0) *emm*1
Emm-type 2nd most frequently detected (%)	5/28 (17.9) *emm*1	5/27 (18.5) *emm6*, *emm*12	5/27 (18.5) *emm*1, *emm*4	5/24 (20.8) *emm*75	3/37 (8.1) *emm*3, *emm*12, *emm*89	5/25 (20.0%) *emm*4

Virulence genes *emm*1 (2013)

CRF	Registration	SpeA	SpeB	SpeC	SpeF	SSA
20130005*	11-jan-13	+	+	+	+	0
20130008*	16-jan-13	+	+	+	+	0
20130009	16-jan-13	+	+	0	+	0
20130015	21-jan-13	+	+	0	+	0
20130021	25-jan-13	+	+	+	+	0
20130023	28-jan-13	+	+	0	+	0
20130025	31-jan-13	+	+	0	+	0
20130027	04-feb-13	+	+	0	+	0
20130028	04-feb-13	+	+	0	+	0
20130031	07-feb-13	+	+	0	+	0
20130032	07-feb-13	+	+	+	+	0
20130037	14-feb-13	+	+	0	+	0
20130039	15-feb-13	+	+	0	+	0
20130046	28-feb-13	+	+	0	+	0
20130089	04-mrt-13	+	+	0	+	0
20130092	08-mrt-13	+	+	0	+	0
20130095	12-mrt-13	+	+	0	+	0
20130097	12-mrt-13	+	+	+	+	0
20130100	14-mrt-13	+	+	+	+	0

* Probably same patient but transfered to UZ Ghent
47/56 emm1 virulence genes analysed, same pattern for 40/47 (85.1%)

PFGE *emm*1 2013 strains, same virulence genes



PFGE type 3 already circulating in Belgium in 1993 (Descheemaeker et al. 2000. J. Med. Microbiol.), most similar to M1 476, a Japanese sepsis isolate

Virulence genes *emm*75 (2014)

CRF	SpeA	SSA	SpeB	SpeC	SpeF
20140011	0	0	+	+	+
20140038	0	0	+	0	+
20140065	0	0	+	0	+
20140085	0	0	+	+	+
20140124	0	+	+	+	+
20140132	0	0	+	+	+
20140133	0	0	+	+	+
20140162	0	0	+	+	+
20140164	0	+	+	+	+
20140180	0	0	+	+	+
20140185	0	0	+	+	+
20140216	0	0	+	+	+
20140226	0	0	+	0	+
20140227	0	0	+	0	+
20140253	0	0	+	+	+
20140271	0	0	+	+	+
20150003	0	0	+	+	+
20150006	0	0	+	+	+

Fatal outcomes due to invasive GAS

Year	Number (%)	*Emm*-types involved
2009	15 (7.8)	*emm1* (n=6), *emm3* (n=4), *emm28* (n=2), *emm4*, *emm5*, *emm77* (n=1)
2010	11 (5.6)	*emm3* (n=3), *emm12* (n=3), *emm87* (n=2), *emm1*, *emm6*, *emm28* (n=1)
2011	18 (9.1)	*emm3* (n=5), *emm89* (n=4), *emm1* (n=3), *emm6* (n=2), *emm9* (n=1), *emm12* (n=1), *emm108*, *emm230* (n=1)
2012	16 (7.4)	*emm1* (n=8), *emm3* (n=2), *emm11*, *emm12*, *emm29*, *emm77*, *emm81*, *emm87* (n=1)
2013	16 (7.4)	*emm1* (n=6), *emm3* (n=3), *emm4*, *emm5*, *emm12*, *emm75*, *emm87*, *emm169*, *emm219*
2014	14 (5.7)	*emm1* (n=6), *emm6* (n=2), *emm3*, *emm22*, *emm29*, *emm44*, *emm77*, *emm89* (n=1)

Remarks and conclusions

- Increasing number of invasive GAS strains submitted to the NRC
- So far no legal obligation for laboratories to submit invasive strains. Difficult to conclude on the observed trends
- *Emm*1, *emm*3, *emm*89, *emm*6, *emm*12 and *emm*28 most detected *emm*-types, accounting for ± 50% of invasive GAS infections in Belgium (Walker et al. 2014)
- Fatal outcomes based on info on CRF<10% and associated with *emm*1 and *emm*3 as previously reported (8-23%, Walker et al. 2014)
- *Emm*1 clone was re-emerging in Belgium in 2013: Highly prevalent in children with invasive GAS (±50%)

Remarks and conclusions (2)

- Presence of virulence genes related to *emm*-type is as previously reported (Commons et al. 2008, Meisal et al. 2010, Plainvert et al. 2011)
- Antibiotic susceptibility still high; resistant *emm*-types similar to those in other European countries (Luca-Harari et al. 2008, Plainvert et al. 2011, Walker et al. 2014)

- **Further information on longitudinal typing of *emm*1 strains: Coppens et al. O226, April 28, 10.00am**

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