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Nicolas Dubois

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UNIVERSITÉ DE MONTPELLIER
FACULTÉ DE MÉDECINE MONTPELLIER-NÎMES

THÈSE

Pour obtenir le titre de

DOCTEUR EN MÉDECINE

Présentée et soutenue publiquement

Par

Nicolas DUBOIS

le 22 Octobre 2021

VENTRICULOSTOMY-RELATED INFECTIONS A PRACTICE SURVEY

Directeur de thèse : Dr Alexandre MAS

JURY

Président :

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Assesseurs :

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Pr Pierre-François PERRIGAULT

PROFESSEUR ASSOCIÉ - Anesthésie réanimation

Dr Alexandre MAS

CHEF DE CLINIQUE - ASSISTANT DES HÔPITAUX - Anesthésie réanimation

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Merci beaucoup **Alexandre** pour tout le mal que tu t'es donné, tu as été toujours très présent, tu as répondu dans la minutes à tous mes messages, tu as été exigeant quand il le fallait. Ça a été un vrai plaisir de travailler avec toi ! Quand je pense que notre première rencontre s'est faite autour d'un ti-punch dans les Antilles, qui aurait cru qu'on en serait là quelques mois plus tard !

Océane merci pour ton travail de relecture, pour ton étrange passion des chiffres et des tableurs Excels !

La famille avant tout

Maman c'est grâce à toi si je suis devenu qui je suis, tu m'as toujours écouté et soutenu, tu es une personne d'une incroyable bienveillance et une grande sensibilité. J'ai beaucoup de chance de t'avoir !

Papa tu es toujours là pour moi, toujours le mot pour rire. On se ressemble beaucoup tous les deux. Il est déjà loin le temps où tu m'avais accueilli dans ton cabinet, je suis très heureux que tu ais pu me transmettre ton expérience, comme à une époque révolue où le père transmettait son métier à son fils.

Marinou je suis tellement fier de toi, tu es devenue une très belle personne, hyperactive, épanouie dans tes études, plein d'amis, un tempérament bien trempé, sportive, qui aime la fête... Tu as tout pour toi !

Sacha je pense qu'on se complète bien l'un l'autre. Tu déborde d'énergie et de motivation, tu es la personne la plus forte que je connaisse, tu as toujours un projet en rêve, et tu arrives toujours à le concrétiser, j'ai l'impression que tu n'as pas de limite. Avec toi je sais que ma vie sera une aventure. Je t'aime.

Mamie toujours accueillante, d'une grande sensibilité, une grande gourmande ! Ton plus grand plaisir est de faire manger tes invités à quatre fois leur faim !

Papy Je sais que j'ai beaucoup hérité de toi, de ton tempérament calme en toute circonstance, ta soif de connaissance, ta joie de vivre. Je suis très content car on arrive régulièrement à se voir ces derniers temps, j’espère qu'on se refera un repas en tête à tête prochainement.

Marraine tu as su rester jeune dans ta tête, un brin de folie, toujours de bonne humeur, reste comme tu es !

Julien mon cousin globe trotteur, tu sais profiter de la vie ! Je suis content que tu aies rencontré **Rachel**, vous faites une bonne paire à vous deux ! J'espère qu'un jour tu me feras visiter le Brésil, et peut être qu'on fera du camping sauvage dans la forêt Amazonienne !

Sophie ma tante du bout du monde, je te promets qu'un jour je viendrai te voir en Nouvelle Zélande, et on fera un trek dans les montagnes ensemble. Tu nous manques.

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Gabriel mon « demi-frère » comme j'aimais à le dire, on a passé une partie de notre enfance ensemble, je repense avec émotion à notre cabane dans les arbres au parc Méric ! On ne se voit pas assez souvent mais j'ai l'impression d'être resté très proche de toi.

Thibaut avec toi aussi on en a fait des bêtises quand on était gamin (je ne les écrirais pas ici !), je ne sais pas comment tu as fait pour devenir un adulte équilibré avec tout ce que t'ont fait subir tes frères !

Marc et Geneviève ça fait une éternité mais je me rappelle très bien de mes vacances à Gouvieux et à l'île d'Oléron, j'en garde toujours des supers souvenirs !

Hélène tu as été ma camarade dans cette dure année de PACES, on s'est aidés l'un l'autre, je ne sais pas si j'aurai tenu le coup sans ton soutien. Des épreuves comme celle-là, ça soude les gens à vie ! Je suis ravi que tu aies rencontré **Flo**, c'est quelqu'un qui te correspond parfaitement !

Bertrand, dès que possible je viendrai te voir au Sri Lanka ! Je suis très impressionné de ce que tu es devenu et ce que tu as construit là-bas.

Jonathan je suis très triste que nos chemins se soient séparés, il n'est jamais trop tard pour se retrouver.

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La famille d'Epinal le cœur sur la main, quand on vient chez vous on est accueillis comme des rois, promis je viens fêter Noël avec vous cette année !

Générique

(par ordre d'apparition dans ma vie)

Sébastien je parie que tu ne t'attendais pas à être cité en premier ! Tu es mon plus vieux pote, je suis content qu'on partage encore des passions en commun, on se fait une session musique quand tu veux !

Paul « mi-homme mi-ours, un des batteurs les plus doué de sa génération » les Inrockuptibles, « d'une grande élégance, classe en toute circonstance » GQ magazine

Elias je suis désolé d'avoir dit que les bassistes ne servent à rien, maintenant j'ai compris qu'ils servent à créer un vague bruit de fond, comme un bourdonnement déplaisant dans les oreilles. Donc je retire tout ce que j'ai dit depuis dix ans, mais pourras-tu me le pardonner un jour ?

Karim un personnage torturé et complexe... Je pense que je m'inspirerai de toi pour écrire le personnage principal de mon bouquin ! ;)

Toinou les soirées avec toi prennent toujours une dimension surnaturelle, tu es quelqu'un de très surprenant et très sincère, j'espère qu'on en refera plein d'autres ! (NB : j'ai des photos merveilleuses de toi)

Ivan et Rafi ça fait un bout de temps qu'on se connaît maintenant ! Ce camping où on avait pensé à prendre de l'alcool mais oublié de prendre de l'eau, les foots en escaladant le mur de Joffres, les soirées sur le toît de l'hôtel en construction...

Sabrina (De Courville) la première fois que je t'ai rencontré (il y a bientôt 13 ans !) c'était à une soirée que tu organisais chez toi, je ne sais même plus comment je me suis retrouvé là ! Je suis très content qu'on se soit suivi pendant toutes ces années, et très ému par ton mariage cet été avec Bruno !

Zoé, on s'est rencontré aux cours d'aviation, c'est vieux tout ça ! Et puis tu as été ma sœur de faluche, puis les vacances à Barcelone, puis les skis médecine (et notre appartement à thème qui a gravé les mémoires !)...

Axel pour ces après-midi piscine-billard à la maison de tes parents !

Thomas (Lory) tu fais partie des personnes qui me connaissent le mieux, on a vécu 4 ans sous le même toit, cet appartement en ruine restera gravé dans ma mémoire de la plus belle des façons. Je repense à nos humiliantes parties de ping-pong dans le couloir, notre plante de compagnie Poka, et toutes les plantes que nous avons tuées (malgré la création d'un service de réanimation botanique à la pointe), nos recettes de cuisines à base de 4 quarts et autres produits premiers prix, nos innombrables soirées avec Mehdi, les jeux de la pièce, les séances « audiophile » où tout l'immeuble tremblait au son de « Giorgio » des Daft Punk...

Mehdi combien de fois as tu été baptisé dans notre appartement ? Te rappelles-tu de notre soirée pré-rentrée sur le toît de la fac de sciences à regarder des reportages sur la théorie des cordes ? De nos foots dans la cour de la vieille fac ? De nos excursions dans les Antilles pour aller voir Thomas et passer notre niveau 1 de plongée ?

Isabel je suis très heureux de t'avoir rencontrée, que tu m'aies emmené chez toi en Bolivie rencontrer tes amis et ta famille. On a fait deux superbes colocations ensemble, avec des soirées musiques de folies ! Sans oublier les petites recettes de **Guigui**, qui nous ramenait une bouteille de vin différente tous les jours, j'ai eu un syndrome de sevrage quand je suis rentré à Montpellier !

Enzito je vais me jeter par le balcon ! Je garde un super souvenir de nos vacances en Bolivie, de nos baignades dans la rivière aux crocodiles, de notre périple dans les mines, de la soirée d'anniversaire d'Isa qui a fini comme tu le sais...

Valou en plus d'être un super coloc, tu as été mon partenaire de parapente ! On a passé une super semaine dans les Pyrénées, plein de souvenirs !

Tibère et Néné Qui est chaud pour une Creuze-ball ? Ou un chausson au Nutella de chez Mamie ?

Julie (Litovsky) nos routes se sont séparées mais tu m'as profondément marqué, notre rencontre aura forcément eu un impact sur ce que je suis devenu aujourd'hui.

Nicolas (Langendorfer) Un grand virtuose, un érudit, Nicolas tu es tellement incroyable et modeste avec ça... J'espère que tu m'inviteras pour tester ton piano un de ces quatre !

Dimitri on s'est rencontré d'une façon assez originale, je t'ai transmis ce bout de tissu rouge sans âge, on a fait partie d'une chaîne qui se perpétue encore aujourd'hui. Tout ça n'est que folklore, le plus important c'est que ça m'a permis de te rencontrer.

Gaelle, Laureen, Lisa les filles de la corpo ! Vous nous avez organisé tant de fêtes, de gala, de manades... c'est grâce à vous si on passé une D1 comme ca !

Lara pour ta folie, ta sensibilité musicale, les soirées avec le conteur d'histoire...

Titia pour m'avoir initié à la photographie.

Sabrina (Bryant) comment as tu fais pour nous supporter avec Enzo ? Le taxi qui sonne à la porte pendant qu'on dort encore... Tu es une petite puce surexcitée, tu as plus d'énergie en toi que n'importe qui !

Marie (du Cailar) est-ce que tu te rappelles de nos soirées de P2 ? J'étais triste que tu partes en Erasmus ! J'en ai presque oublié ton visage, je crois que c'est pour ça que je ne te reconnais plus quand je te croise à l'hôpital !

Lorenzo on a passé un externat sans trop apprendre à se connaître, mais je suis très content de t'avoir découvert pendant ces quelques dernières années (et ces vacances en Lozère !)

Marion (Garbay) plus qu'une colocataire, plus qu'une amie, tu es ma confidente, c'est vers toi que je me tourne dès que j'ai une question existentielle, je sais qu'avec toi je peux tout dire ! Tu fais partie des personnes qui me connaissent le mieux.

Ananas la dernière fois qu'on a fait du volley ensemble je me suis cassé le bras, j'attend toujours ma revanche !

La coloc de Perpi (alias la coloc des super héros) quatre femmes rien que pour moi, c'est trop ! Pour ces soirées avec toi Sara devant the Knick, et toi Amélie la commère qui connait absolument tous les potins sur tout le monde !

Matthias très heureux que nos chemins se soient croisés, je pense que personne d'autre ne pouvait mieux te comprendre que moi (l'inverse est probablement vrai aussi), toi seul possède cet état d'esprit, où les raisonnements logiques poussés à l'extrême côtoient l'absurde et l'anticonformisme. Notre colocation était une expérience sociale, le plus joyeux et bordélique lieu de vie que j'ai connu ! **Marion** je suis très content de t'avoir rencontrée, tu es tout le temps de bonne humeur, tu es drôle, tu es la meilleure chanteuse que je connaisse, et depuis que tu es de retour mon copain est enfin heureux et (un peu plus) équilibré.

Yann tu m'as toujours accueilli chez toi avec le sourire, j'ai passé d'excellentes soirées en ta présence, on n'a pas vraiment été en colocation ensemble, mais j'ai l'impression que c'est tout comme !

Corentin de tous mes potes c'est toi qui me fait le plus rire, tu es toujours partant pour n'importe quelle idée (même les pires), je pense sincèrement que tu es doué d'une intelligence exceptionnelle mais je ne sais pas si tu t'en rends compte (?). Je ne garderai que des bons souvenirs de notre colocation (hormis ta recette de pâtes à la crème fraîche). NB : Bientôt je serai un grand saxophoniste comme toi !

Alexis trop drôle nos soirées JDR ! Merci de m'avoir fait découvrir ça !

Estelle pour ton humour tout en finesse (comparé à celui de Paul), tes éclats de rires en permanence, car tu rends mon Paulo heureux.

Serena pour ta joie, pour cette soirée au Red Line, pour tes talents de cuisinière, pour ton goût prononcé pour les jeux de société intellectuels.

Calou, non je ne te déteste pas contrairement à ce que Paul aime répéter ! Bon sens de l'humour et auto dérision, tu compenses habilement l'absence de finesse de Paul.

Afaf Merci pour tout ! Je n'ai pas fini ma formation mais grâce à toi j'ai conduit un avion seul à bord !! Une expérience incroyable, je me repasse la vidéo régulièrement ! Tu es parfaite Afaf, tu es drôle, sympa, hyper sociable, je pouvais pas rêver mieux comme instructeur de vol !

Julie (Borovik) tu es incroyablement et merveilleusement folle, tu aimes rire (fort), tu aimes la philosophie (et les philosophes), tu sais très bien raconter tes histoires mais tu sais encore mieux écouter celles des autres. Tu es une très belle personne Julie.

Arthur mais qui aurait pensé qu'on finisse en colocation ensemble ! Quel concours de circonstance ! Trop intelligent pour le commun des mortels, je ne pensais pas qu'on pouvait travailler autant avant qu'on vive ensemble, tu aimes malgré tout les petits plaisirs simples : cultiver ton pied de tomate, manger tes corn flakes le matin, hurler dans l'appart quand tu rentres bourré de soirée... ;)

Jules un exhibitionniste de talent, un grand photographe de rue, la mascotte de la Gay pride, un super co-interne... tu as beaucoup de casquettes ! Perpignan nous a soudé, dans la joie et la douleur. Je voulais juste te rappeler que tu ne dois qu'à l'intervention d'Ali de ne pas être derrière les barreaux aujourd'hui !

Laura merci de m'avoir accueilli dans ton château à Millau (!), pour ta bonne humeur, pour ton petit accent qui nous fait voyager ! On se le fera la prochaine fois ce festival de jazz à Millau !

Thomas (Odonnat) l'escroc du siècle ! Le Arsène Lupin de l'anesthésie ! Les Antilles n'ont jamais aussi bien été représentées en Métropole, je t'ai découvert à Perpignan, tu étais déjà magnifique à l'époque (on en reparle de cette garde qui commence à midi, ou de ce satané téléphone de garde que tu éteignais avant d'aller dormir ?), mais tu n'as jamais autant brillé qu'au DAR A ! Heureusement que tu étais là, avec qui j'aurais pris mes petits déjeuners post staff sinon ?

Marion une grande fêtarde, une grande sportive, tu es plus bronzée en hiver que moi en été ! A quand la prochaine paillote ?

Ma petite **Jade**, tu es sincère, tu ne sais pas cacher tes émotions, (on lit en toi comme dans un livre ^^), on a passé un super semestre à Perpignan, encore foufou des premiers semestres, soudés comme un bloc face à l'adversité (tu sais de qui je parle !). J'espère que tu continueras à organiser de merveilleuses fêtes dans la maison de ta mère !!

Kevin alias « le papa », tu nous as maternés comme des gamins insupportables, tu nous à défendus même quand on était indéfendables, je pense au fond que tu étais probablement pire encore quand étais jeune semestre ! Ces apéros en sortant du travail, qui finissait à 5h du matin au Fizz, on a pu voir la bête qui se cachait derrière ce visage d'ange !

Clément (Anin) j'ai trouvé plus grand que moi (!), heureusement que je te mets la misère au squash sinon j'aurai eu des complexes !

Ludo tu es une énigme pour moi, je ne sais pas vraiment comment fonctionne ce cerveau, à la fois le plus intelligent et le plus stupide de mes potes ! Les tournois de baby foot du DAR B, les « paint ball » à la réa de Perpi, j'espère que tu as apprécié les fonds d'écran qu'on à laissé dans ton bureau du DAR B !

Lucille ma sauveuse ! Grâce à toi je suis complètement réparé =)

Nacim tu me fais penser à Freddy Mercury sans moustache ! Je me rappelle de cette soirée à Perpignan où on est tous allé dormir dans la chambre de l'interne de garde à même le sol, tu avais essayé de me perfuser dans un grand moment de lucidité, et tu m'avais éclaté ma veine (alors que j'ai des autoroutes!!). Et cette journée tout à fait normale en réanimation où tu avais fini pieds et poings liés à une chaise pour te raser la tête !

Elodie, un fort tempérament, il ne faut l'énerver notre Elodie ! Tu étais clairement la plus dure à cuire de nous tous, notre petite Katnis Everdeen ! Une fois qu'on t'a apprivoisée tu es douce comme un agneau ! Des co-internes comme toi on en redemande !

Victor te rappelles-tu de ces tournois de corbeille-basket au DAR A ? De nos montages photos en fond d'écran de l'ordinateur de la salle de staff ? Quand on part avec toi en soirée on ne sait jamais quand on revient, ni dans quel état ;) !

Jordi le beau gosse de Perpi ! Ces coups de stress qu'on s'est pris ensemble dans cette réa, heureusement qu'on a bien décompensé à l'internat ! Est ce que tu te rappelles de cette soirée de fin de semestre avec ce magnifique tir de feu d'artifice juste au-dessus de l'hôpital ?

Fabien on savait exactement dans quelle pièce tu étais passé grâce à ce superbe parfum de vapoteuse qui foutait la nausée à tout le monde ! Un jour les cheveux longs, le lendemain rasé à blanc, je crois que j'ai fait une syncope ce jour là !

Chirine derrière ton petit air de fille bien sage se cache ton double maléfique (dark chichi) qui apparaît après 3 verres, gare à vous si vous la croisez !

La coloc de Versailles, on a vécu le premier confinement tous ensemble, mais on a continué à vivre malgré tout, à faire nos soirées entre nous le vendredi soir, à faire des gros repas ensemble, faire des séances cinéma... Vous m'avez tous aidé et soutenu après mon accident, vous m'avez probablement vu dans mon pire état ! Merci pour tout ça, je me rends compte que j'ai eu beaucoup de chance qu'on soit tous ensemble à ce moment-là.

Thomas (Laumont) pour ton implication dans la terraformation de Mars, beau projet qui mérite tous nos applaudissements, et pour avoir mis le feu à nos soirées avec tes platines !

Silvia ma petite italienne de compagnie qui a égayé notre quotidien pendant ces quelques mois en France.

Et tous les autres co-internes : **Aude, Geoffrey, Nicolas, Marc, Mathilde, Arnaud, Alexandre, Thomas, Jacques, Chloe, Marie, Baptiste, Youcef, Marwane, Laurine, Ramla, Pauline...**

Merci à l'équipe d'anesthésie pédiatrique d'avoir cru en moi, notamment **Chrystelle** et **Philippe** !

A toute **l'équipe du bloc de Saint Eloi** qui m'a accueilli à bras ouvert, j'en garde d'excellents souvenirs.

Merci à tous ces chefs qui m'ont marqué : **José** qui ne décline jamais une invitation au bar, **Cindé** qui vient en garde en boitant comme une petite vieille, **Wathek** ton nom est devenu synonyme de « gueule de bois », **Aziz** qui va négocier avec la police pour éviter la garde à vue pour mes co internes en état d'ébriété.

Pour ces médecins qui sont des modèles pour moi : **Pauline** pour ton savoir encyclopédique et ton sang froid en toute circonstance, **Olivier de Matteis** l'homme qui a organisé le sauvetage d'un bus d'enfants, **Pr Bringer** pour qui j'ai le plus grand respect, **Pr Lequelec** l'un des plus grands médecins que Montpellier est connu.

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Introduction

External ventricular drain (EVD) is one of the most common neurosurgical procedures. It allows the monitoring and treatment of intracranial hypertension and is used for patients with diffuse subarachnoid haemorrhage, after severe traumatic brain injury or for tumoral hydrocephalus.

Ventriculostomy related infection (VRI) is one of the main complications of EVD, the incidence of VRI is around 10% (1) (between 2 and 22% depending on the study (2–9)), with an incidence of 6.3 to 11,4 per 1000 catheter days (10,11). VRI is a serious concern, as it may cause neurological sequelae (12) (relative risk 5.3 (13)), longer hospitalization and increased costs (6). The management of these infections is complicated and requires the cooperation of several specialists (neurosurgeons, intensivists and infectious diseases specialists).

The diagnostic methods and management of VRI are very heterogeneous, because of a lack of evidence. To this day, there is no European or French recommendation. The United States shared their recommendation in 2017 (14), but several factors such as bacterial ecology may not be comparable between the different countries (15), which makes these recommendations less pertinent for European countries.

The aim of our study is to evaluate the practices of neuro intensive care units in french-speaking European countries, in order to help create future French recommendations.

Materials and methods

We conducted a practice survey on the management of EVD using an online questionnaire (Supplemental Data 1). This questionnaire was sent with Google Forms software to intensive care units specialized in neurology and neurosurgery, in french-speaking european countries, via the "Association de Neuro-Anesthésistes-Réanimateurs de Langue Française" (ANARLF). The participants received up to 3 reminders by email in order to obtain a better participation.

This survey was a multiple choice questionnaire with 35 questions on four main topics, the first part dealt with the management of EVD : the place of installation (operating room or intensive care unit), antibiotic prophylaxis during placement, frequency of tubing and collection system changes, protection of the proximal valve, systematic culture of EVD during removal, EVD impregnated with anti-infectives, EVD tunneling.

The second part was dedicated to the diagnosis of VRI : differentiating between infection and colonization, Cerebrospinal fluid (CSF) lactate level, blood procalcitonin level, cell index, 16S RNA PCR, CSF sampling site, brain imaging.

The third part concerned the management of VRI : management of colonization, management of infection, empiric antibiotic therapy, antibiotic therapy for Methicillin-sensitive Staphylococcus, antibiotic therapy for Methicillin-resistant Staphylococcus, duration of antibiotic therapy, antibiotic dosages in CSF, evaluation of the efficacy of antibiotic therapy, delay before placement of an internal ventricular shunt.

The fourth part focused on intraventricular antibiotic therapy : indication, dose, duration, dosage of the antibiotic in the CSF, duration of clamping of the EVD, frequency of administration.

Answers were collected between January and June 2021, only one response per institution was taken into account. By completing the questionnaire, participants consented to the analysis of their responses and the publication of the data. Data collection and processing was carried out by the University

Hospital of Montpellier (France), all data were anonymized. The analysis of the results was realized with Google Sheets software.

Results

The questionnaire was sent to 36 university hospitals, 34 of them (94.4 %) completed the questionnaire : 30 hospitals were in France, 3 in Belgium and 1 in Switzerland.

Management of EVD

The majority of centers (85,3 %) placed their EVDs exclusively in the operating room. Most of the participants (61,8 %) never used antibiotic prophylaxis during the placement of EVDs and 23,5 % of them used it systematically (Table 1). The majority of participants (79,4 %) never used anti-infective impregnated EVD catheters ; for those participants who used them, the primary indication (57 %) was EVD replacement due to infection. The majority of EVD catheters were systematically tunneled under the skin (73,5 %), over a distance greater than 5 cm (60,7 %).

The majority of centers (94,1 %) did not regularly and systematically change the EVD tubing and collection system. Most participants (73,5 %) protected the proximal tap of the EVD : 35 % in a box, 14,7 % in a dry compress or absorbent dressing pad, 11,8 % in a compress soaked with antiseptic, 11,8 % under the capeline.

When removing EVD in the absence of suspected infection, 38,2 % of the centers never put them in culture. On the other hand 32,5 % of the centers systematically cultivated their EVDs after their removal, if this culture was positive 66.7% of participants collected a CSF sample to confirm the result ; the majority of participants (82,4 %) started antibiotic therapy only in presence of an altered clinical status or CSF analysis.

Diagnosis of VRI

The majority of the centers (55,9 %) used standardized definitions according to a service protocol to discriminate between infection and colonization of EVD, and 44,1 % of centers left the diagnostic criteria to the discretion of the physician.

In case of suspected VRI, 42,4 % of participants collected CSF from the patient line stopcock (proximal stopcock) as the first intention, and 36,4% of participants collected CSF from the drip chamber (Supplemental data 1 : figure).

Most of the participants (67,6 %) considered the cell index (leukocyte/erythrocyte ratio in blood and CSF) to suspect a VRI. The majority of participants (61,8 %) did not consider the CSF lactate level to suspect a VRI, in the same way most of the participants (82,4 %) did not consider the blood procalcitonin level to suspect a VRI. In case of suspected VRI, no participant systematically performed 16S RNA PCR on the CSF, 79,4 % of participants sometimes did it, and 20,6 % never did so.

In case of suspected VRI, only 26,5 % of participants performed brain imaging systematically, and 67,6 % performed imaging occasionally. Most of the time (83,3 %) brain imaging was a CT scan on first intention, participants looked for ventriculitis (93,5 %), ventricular dilatation (64,5 %) and abscess (54,8 %).

Management of VRI

In case of suspected EVD colonization, 78,1 % of participants performed a new CSF sampling from the patient line stopcock (proximal stopcock), 43,8 % performed a change of the external circuit of the EVD before performing the CSF sampling.

In case of suspected EVD infection, a large majority of participants (70,6 %) changed the EVD after 48-72h of antibiotic therapy, 20,6 % changed the EVD immediately.

In case of suspected EVD infection, only 8,8 % of participants initiated a single empiric antibiotic therapy, a large majority of participants (91,2 %) used a

combination of several empiric antibiotics. All antibiotic combinations included an antibiotic effective against staphylococci combined with an antibiotic effective against gram-negative bacilli. The most commonly used staphylococcal effective antibiotics were Linezolid (48,5 %) and Vancomycin (36,4 %) (Figure 1). The most commonly used antibiotics effective against GNB were Meropenem (39,5 %), Cefotaxime (26,3 %), and Ceftazidime (18,4 %) (Figure 2).

In case of Methicillin-sensitive Staphylococcus infection, the most frequently used antibiotics were Oxacillin (44,1 %) and Cefotaxime (23,5 %) (Figure 3). Some of the participants (20.6%) used a combination of antibiotics including Rifampicin.

In case of Methicillin-resistant Staphylococcus infection, 52,9 % of participants used Linezolid, and 44,1 % used Vancomycin.

For coagulation-negative Staphylococcus infection, most of the participants (63,6 %) used antibiotic therapy for 8-14 days (Table 2). For Staphylococcus aureus infection, most of the participants (63,6 %) used antibiotic therapy for 8-14 days. In case of Propionibacterium Acnes infection, the majority of participants used antibiotic therapy for 8-14 days. In case of Pseudomonas Aeruginosa infection, 45,5 % of participants used antibiotic therapy for 15-21 days, and 39,4 % for 8-14 days. In case of gram-negative infection, 57,6 % of participants used antibiotic therapy for 15-21 days, and 36,4 % for 8-14 days.

If intravenous antibiotic therapy was initiated, 26,5 % of participants never performed CSF antibiotic dosing, 61,8 % performed it occasionally, and only 11,8 % performed it routinely. The effectiveness of antibiotic therapy was assessed by clinical status alone by 14,7% of participants, on the other hand 41,2% of participants systematically monitored blood markers (leukocytes, CRP, PCT) to assess the effectiveness of antibiotic therapy, and 76,5% of participants systematically performed CSF analysis (84,6 % of them repeated CSF analysis until culture negativation, 30.1% of them practiced a CSF analysis at the end of antibiotic treatment).

In case of VRI, the time required before the installation of an internal ventricular shunt was 7 days after culture negativation for 29 % of participants, 2-7 days after culture negativation (19,4 %), a minimum of 7 days of antibiotic

therapy (12,9 %). This duration had to be adapted according to the type of bacteria for 38,7 % of the participants.

Intraventricular antibiotic therapy

Participants used intraventricular antibiotic therapy in case of failure of intravenous antibiotic therapy (67.6%), in case of resistant germs (47,1 %), or in case of ventriculitis on imaging (52,3 %). Only 11,8 % of participants never used intraventricular antibiotic therapy. No participants used the intraventricular route in a systematic way.

Most participants (63,3 %) injected the same standard dose for all patients. On the other hand 26,7 % adjusted the administered dose according to the antibiotic dosage in the CSF, 13,3 % adjusted the administered dose according to the minimum inhibitory concentration of the bacteria. After intraventricular antibiotic injection, all participants clamped the EVD, and the majority (76,7 %) clamped the EVD for 15 to 60 minutes.

For 34,5 % of the participants the frequency of injection of intraventricular antibiotic therapy should be one dose per day, 32,7 % adapted the frequency of injection to the quantity of CSF drained, 21,8 % adapted the frequency of injection to the dosage of antibiotic in the CSF. Before injecting a new dose of intraventricular antibiotic, most participants never (43,3 %) or rarely (40 %) performed CSF antibiotic dosing.

The duration of intraventricular antibiotic therapy was less than 3 days for 40,7 % of participants, and between 3 and 7 days for 40,7 % of participants.

Figures

Table 1 : semi-quantitative answers

	Never	Less than 50% of cases	More than 50% of cases	Always
Use of antibiotic prophylaxis during EVD placement	61,8 %	11,8 %	2,9 %	23,5 %
Use of EVD impregnated with anti-infectives	79,4 %	14,7 %	-	5,9 %
EVD tunneling	17,6 %	-	8,8 %	73,5 %
Systematic culture of EVD during removal	38,2 %	23,5 %	5,9 %	32,5 %
Performing of 16S RNA PCR for the diagnosis of VRI	20,6 %	67,6 %	11,8 %	-
Brain imaging in the case of VRI	5,9 %	32,4 %	35,3 %	26,5 %
Antibiotic dosages in CSF in case of intravenous antibiotic therapy	26,5 %	38,2 %	23,5 %	11,8 %
Antibiotic dosages in CSF in case of intraventricular antibiotic therapy	43,3 %	40 %	16,7 %	-

EVD : external ventricular drain
CSF : cerebrospinal fluid

Table 2 : Duration of intravenous antibiotic therapy

	7j	8-14j	15-21j	> 21j
Coag. neg. Staph.	15,2 %	63,6 %	21,2 %	0 %
Staph. Aureus	6,1 %	63,6 %	27,3 %	3,0 %
P. Acnes	12,9 %	51,6 %	25,8 %	9,7 %
P. Aeruginosa	0 %	39,4 %	45,5 %	15,2 %
Gram neg. bacteria	3,0 %	36,4 %	57,6 %	3,0 %

Figure 1 : Empiric antibiotic therapy in case of suspected IRV

Anti-staphylococcal antibiotic

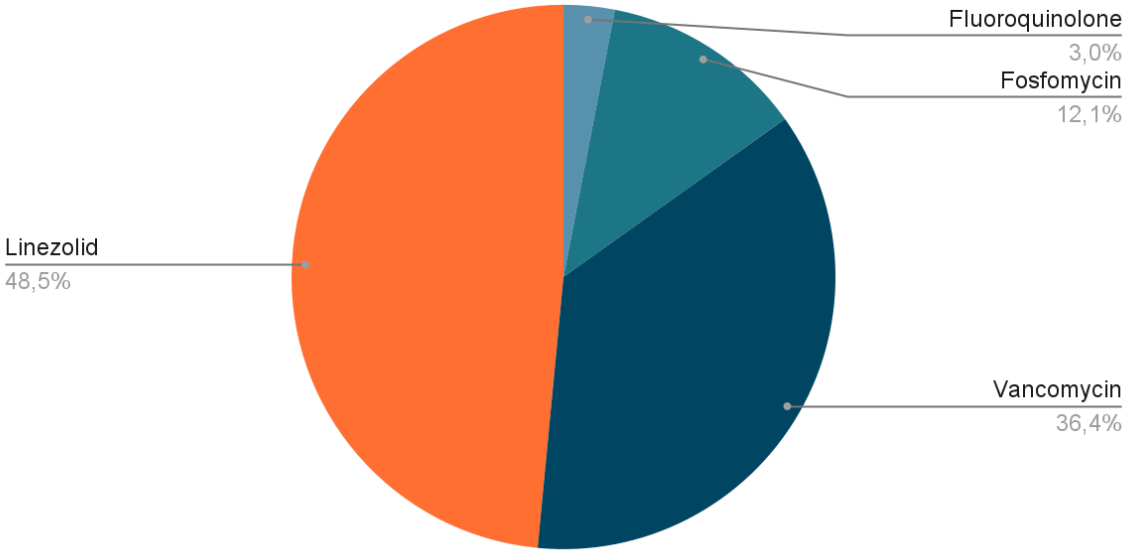


Figure 2 : Empiric antibiotic therapy in case of suspected IRV

Anti gram negative bacteria antibiotics

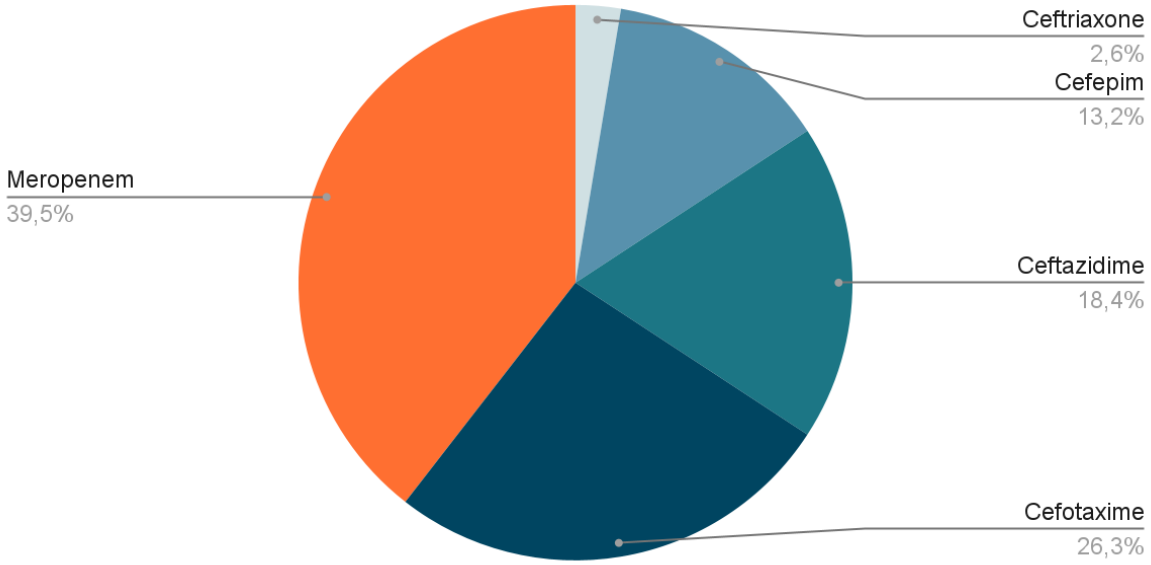
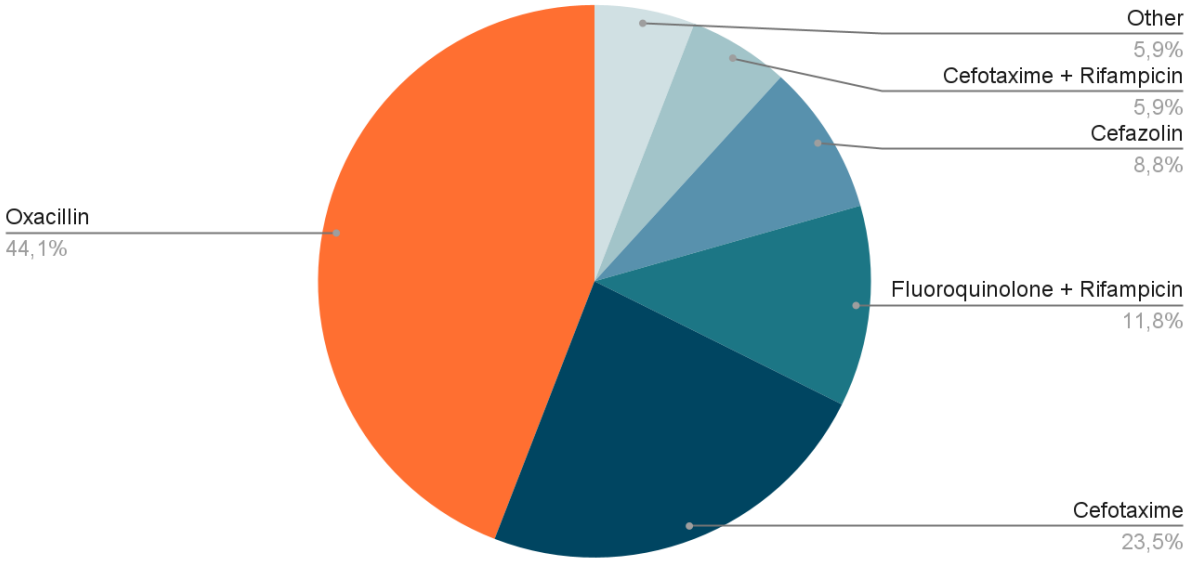


Figure 3 : Antibiotherapy for metycillin-susceptible Staphylococcus IRV



Discussion

Management of EVD

EVD management has a decisive impact on VRI prevention. This management has improved significantly over the last 20 years, which led to a decrease in the rate of VRIs (18.3 per 1000 catheter days before the 2000s, to 10.5 per 1000 catheter days after the 2000s) (11).

In our study, the vast majority of centers place their EVDs in the operating room. Most studies (6,7,16) did not find an association between the location of EVDs placement (operating room or ICU) and the rate of VRI. However, Clark et al. (16) found a higher rate of subdural empyema, bone flap infection and brain abscess for EVDs placed in ICU. Some studies (9,11) find that VRI occur mainly in the days following the placement of EVDs, which suggests that most VRI might be due to aseptic errors during the placement of EVDs.

The use of antibiotic prophylaxis during EVD placement has been a long debated topic. The US recommendations (14) encourage antibiotic prophylaxis, whereas the French recommendations (17) advise against antibiotic prophylaxis. In this study it appears that there is no consensus among our participants on the subject of antibiotic prophylaxis, 61% of them do not use antibiotic prophylaxis according to French recommendations. Three meta-analyses (18–20) based only on randomized controlled studies show a decrease in VRI rate with antibiotic prophylaxis with an odd ratio of 0.52. It should be noted that the use of antibiotic prophylaxis may favour VRI with resistant germs (MRSA, Serratia) or opportunistic germs (Candida species) (21,22).

The majority of participants in our study never use an anti-infective impregnated EVD catheter. However, a number of studies including a good quality randomized controlled trial by Zabramski et al. (23), indicate that the use of an anti-infective-impregnated EVD catheter reduces the rate of VRI. Several meta-analyses (11,20) conclude a reduction in VRI with an odd ratio between 0.19 and 0.37.

Most participants tunnelize the catheters over a distance of more than 5cm. Omar et al. (24) found a large decrease in VRI in patients with tunnelings longer than 5 cm compared with tunnelings shorter than 5 cm (odd ratio 0.18).

Routine and regular change of the EVD tubing and collecting system has not been tested in any study, however, it is known that increased handling and opening of the closed system causes an increase in VRI (15,25).

Diagnosis of VRI

The definition of VRI is not consensual, Ramanan et al (11) performed a meta analysis of 35 studies and found a rate of reported VRI highly correlated with the definition of VRI used. Using the Centers for Disease Control definition (26) the average VRI rate is 8.8/1000 catheter-days. But 50% of the studies define VRI only by a positive culture, which leads to an overdiagnosis (VRI rate in these studies at 11.5/1000 catheter-days) because colonization and contamination are also included. In order to help find a consensual definition, Lozier et al. (1) suggested a diagnostic method that differentiates contamination, colonization, ventriculostomy related infection and ventriculitis. The 2017 US recommendation (14) provides a diagnostic method that is very similar to Lozier et al.

A minority of participants in our study use the CSF lactate assay to aid in the diagnosis of VRI. However recent large meta-analyses (27,28) found a sensitivity of 93-97% and a specificity of 94-96%, with a better ROC curve than conventional markers (CSF glucose, CSF/plasma glucose quotient, CSF protein, and CSF total number of leukocytes). When studying the diagnostic value of CSF lactate in patients with EVD, the specificity is not as good (Wong et al. found a positive predictive value of only 60%, and a negative predictive value of 100% with a lactate cutoff of 4mmol/L) (29).

In case of meningitis, PCT seems to have a very good specificity but a low sensitivity (Schwartz et al. find a specificity of 100%, better than the leukocyte count or the lactate level in the CSF) (30).

The cell index was defined in 2004 by Pfausler et al (31) by the formula (CSF leukocyte / CSF erythrocyte) / (blood leukocyte / blood erythrocyte), the studies on this index are very few and strongly discordant (32). In our study, the majority of participants used this index for the diagnosis of VRI despite the low level of evidence.

Participants rarely use 16S RNA PCR, however Banks et al. (33) found an excellent sensitivity. A great advantage of this technique is that it allows very fast results, which can be useful with some germs of difficult or slow culture (Propionibacterium Acnes or some GNB).

In case of suspected VRI, brain imaging is used to diagnose ventriculitis and to look for complications (brain abscess, subdural empyema, hydrocephalus, thrombosis) (34). Only 1/3 of the participants in our study do imaging systematically. CT is more easily performed but magnetic resonance imaging is more sensitive for detecting ventriculitis (35). Today, all neuro ICUs in the ANARLF network have access to MRI, however in our study the vast majority of participants perform CT as first line, this is probably due to the fact that this imaging is more easily and quickly available.

Management of VRI

In a recent meta-analysis of 35 studies (11), the most frequent bacteria in VRI are Staphylococci which represent 54% of cases, followed by gram-negative bacteria at 35%. It is notable that the most frequent GNB (Acinetobacter species, Enterobacter species and Pseudomonas Aeruginosa) are more resistant germs than the other enterobacterias. However, the bacterial ecology is different from one country to another, for example the most frequent germs in Europe are coagulation-negative Staphylococci (10,25), while in the United States the most frequent germs in some studies are GNB (6,13). Thus, it is necessary to take into account the local bacterial ecology to start a probabilistic antibiotic therapy.

In our study, almost all participants used a bi-antibiotic therapy in case of VRI, including an anti-staphylococcal antibiotic (mainly Linezolid or Vancomycin)

and an antibiotic effective against gram-negative bacteria (mainly Meropenem, Cefotaxime, Ceftazidime or Cefepime).

Regarding the gram-negative antibiotic, the majority of participants chose an antibiotic effective against Pseudomonas Aeruginosa (Meropenem, Ceftazidime, or Cefepime), which is also recommended by the Infectious Diseases Society of America (14). Both Ceftazidim and Cefepime have modest meningeal penetrations (36,37), but appear to be effective in Pseudomonas Aeruginosa meningitis (38,39). It should be noted that both antibiotics can have neurological side effects (confusion, myoclonus and seizure) (40). However, about 30% of the participants preferred to use Cefotaxime or Ceftriaxone to target GNB. This may be explained by the bacterial ecology of their ward with low levels of Pseudomonas Aeruginosa. These two antibiotics have a modest distribution in the CSF (41), but have been shown to be effective against GNB meningitis (42). There is an increase in the rate of VRI with multi-resistant gram-negative bacteria. The most common is Acinetobacter species (11) which accounts for 9% of VRI, with an increasing incidence (43) and has become the most common germ in some countries (44). The probabilistic antibiotic therapy recommended by the Infectious Diseases Society of America (14) is Vancomycin combined with Cefepime or Ceftazidime or Carbapenem. The problem is that using Cefepime or Ceftazidime only treats 10% of Acinetobacter (37), due to antibiotic resistance (45). It is therefore essential to know the bacterial ecology of the department before prescribing probabilistic antibiotic therapy.

For Methicillin-sensitive Staphylococcus VRI, the most commonly used antibiotic by our participants is Cloxacillin, which is also the antibiotic recommended by Infectious Diseases Society of America (14). About 20% of our participants use a combination of antibiotics including Rifampicin. Rifampicin has excellent penetration into CSF, even in the absence of meningeal inflammation (46), and has good penetration into bacterial biofilms that may form on contact with materials (47). On Rifampicin-susceptible Staphylococci, this antibiotic seems to be effective (48), but should never be used as monotherapy to avoid the development of resistance (49). Rifampicin is very useful in case of infection of equipment, especially if it is impossible to remove it (14).

Concerning Methicillin-resistant Staphylococci, the Infectious Diseases Society of America (14) strongly recommends the use of Vancomycin as a first-line treatment, but in our study, the majority of participants preferred to use Linezolid. This non-use of Vancomycin can be explained by several reasons. The first reason is its complexity of use, as it requires regular dosing to be sure of the efficacy, an underdosing of Vancomycin leads to treatment failures (50). It seems that the target blood level of Vancomycin is 15-20 µg/mL (49). Another reason is the risk of adverse effects in patients with organ dysfunction. Another problem with Vancomycin is its poor penetration into the CSF, which can sometimes be insufficient in cases of moderate meningeal inflammation (51). In contrast to Vancomycin, Linezolid is simpler to use and has an excellent penetration in the CSF close to 80% (52). Many articles show the efficacy of Linezolid in case of VRI with Methicillin-resistant Staphylococcus (53–55).

There are no randomized controlled trials comparing duration of antibiotic therapy in care-related meningitis. The Infectious Diseases Society of America (14) recommends an antibiotic duration of 10-14 days (possibly up to 21 days for some GNB). If cultures remain positive despite antibiotics, the IDSA recommends maintaining 10-14 days of antibiotics after the last positive culture.

Intraventricular antibiotic therapy

Vancomycin is known to have poor penetration into the CSF (56), similarly Aminoglycosides do not cross the blood-brain barrier (15), they have a penetration rate in the CSF < 1% (57).

The indications for intraventricular antibiotic therapy are not consensual, some authors recommend it in case of failure of intravenous antibiotic therapy (14,58), in case of impossibility to remove infected material (14,58), in case of ventriculitis (59), in case of infection with a highly resistant germ (58), in case of inability to achieve antibiotic concentration in the CSF with non-toxic doses of antibiotic (60).

Regarding intraventricular antibiotic therapy, there is only one randomized study in adults on a very small sample (51), very few prospective studies, current

recommendations are mainly based on expert opinion (14,61). Most studies show faster CSF sterilization using a combination of intraventricular and intravenous antibiotics than intravenous alone (60,62). Wilki et al. (62) also showed a decrease in total systemic antibiotic duration and a decrease in hospitalization time. The two most commonly used intraventricular antibiotics are Vancomycin and Gentamicin (37,51,60,61,63).

We decided that this questionnaire would be sent to 36 centers of the ANARLF network, specialized in neurological intensive care, which allows to have the answers only from expert centers. A strong point of this study is its response rate of 94.4%, which allows a correct representation of the current practices of French-speaking ICUs.

A limitation of this study is that all the participants are anesthesiologists or intensivists, whereas other specialties are concerned by the management of VRI. Thus this questionnaire will be sent to neurosurgeons and infectious diseases specialists in the near future

Conclusion

This study reveals that the management of ventriculostomy-related infections is highly heterogeneous between specialized centers in French-speaking Europe. This is due to the fact that the literature is not extensive on this subject, and current knowledge is mainly based on retrospective and small sample studies. It seems necessary to conduct randomized studies on this subject. European and French recommendations should help physicians to standardize their practices.

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Conflicts of interest

No conflicts of interest.

Supplemental data 1 : Online questionnaire

La dérivation ventriculaire externe (DVE) est une technique régulièrement utilisée dans les cas d'hydrocéphalie aiguë ou pour le traitement et le monitorage de l'hypertension intracrânienne.

Les infections représentent l'une des principales complications de l'utilisation des DVE. Bien que ces infections soient fréquentes, il n'existe pas de critères diagnostiques standardisés et la prise en charge est très peu codifiée.

Cette situation a poussé l'IDSA (Infectious Diseases Society of America) à publier des recommandations (1) en 2017. Il n'existe pas de recommandations françaises à ce jour.

Ce questionnaire aborde plusieurs points clés dans la prise en charge des infections sur DVE. Le premier point concerne les critères cliniques et examens complémentaires nécessaires afin d'établir le diagnostic d'infection sur DVE. Un deuxième point concerne la prise en charge des infections sur DVE, l'antibiothérapie et la gestion du matériel infecté. Un dernier point concerne la gestion des DVE au quotidien et notamment la prévention des infections.

Cette enquête de pratiques professionnelles est à considérer en complément du travail réalisé par le Dr BEAUFILS Béranger (External ventricular drain management in neuro-intensive care units: a French survey, 2019). L'objectif est d'évaluer les différences de pratiques au sein de nos hôpitaux, en vue de la création de prochaines recommandations françaises.

(1) Clinical Infectious Diseases, Volume 64, Issue 6, 15 March 2017, Pages e34–e65, https://doi.org/10.1093/cid/ciw861

1) Quelle est votre spécialité ?

a) Réanimateur

b) Neurochirurgien

c) Infectiologue

d) Autre

Diagnostic

2) Dans votre unité, comment différenciez-vous une infection et une colonisation de DVE ?

a) Utilisation de définitions standardisées

b) Critères diagnostiques laissés à l'appréciation du praticien

Pour la suite du questionnaire, nous considérerons les termes "infection" et "colonisation" tels que définis dans les recommandations IDSA 2017 (1) :
Infection : une ou plusieurs cultures positives de LCS, associées à une ou des anomalies du LCS (une pléïocytose du LCS et/ou une hypoglycorachie, ou une augmentation du nombre de cellules), ainsi que des signes cliniques évocateurs de ventriculite ou méningite
Colonisation : multiples cultures de LCS ou d'examens directs de LCS positifs, associés à une cellularité du LCS normale, une glycorachie normale et une une protéinorachie normale, ainsi qu'une absence de signes cliniques évocateurs de ventriculite ou méningite

(1) Clinical Infectious Diseases, Volume 64, Issue 6, 15 March 2017, Pages e34–e65, https://doi.org/10.1093/cid/ciw861

3) En cas de suspicion d'infection sur DVE, le taux de lactate dans le LCS influence-t-il votre prise en charge ?

a) Oui

b) Non

4) En cas de suspicion d'infection sur DVE, le taux de procalcitonine sanguine influence-t-il votre prise en charge ?

a) Oui

b) Non

5) En cas de suspicion d'infection sur DVE, l'index cellulaire (ratio leucocytes/hématies dans le sang et LCS) influence-t-il votre prise en charge ?

a) Oui

b) Non

6) En cas de suspicion d'infection sur DVE, pratiquez-vous une analyse PCR ARN 16S sur le LCS ?

a) Jamais

b) Parfois (< 50% des cas)

c) Souvent (> 50% des cas)

d) Systématiquement

7) En cas de suspicion d'infection sur DVE, sur quel site effectuez-vous le prélèvement de LCS en première intention ?

a) Sur le robinet de la ligne patient (proximal)

b) Sur le site de prélèvement/injection sans aiguille

c) Sur le robinet du système (distal)

d) Sur le robinet de la chambre d'écoulement

8) En cas de suspicion d'infection sur DVE, réalisez-vous une imagerie cérébrale ?

a) Jamais

b) Parfois (< 50% des cas)

c) Souvent (> 50% des cas)

d) Systématiquement

8bis) Que recherchez-vous à l'imagerie ?

a) Une ventriculite

b) Un abcès

c) Une dilatation ventriculaire

d) Autre

8ter) Si vous réalisez une imagerie cérébrale pour suspicion d'infection sur DVE

a) IRM en première intention

b) TDM en première intention

Gestion des DVE

9) Au sein de votre unité, dans quel(s) lieu(x) est/sont posée(s) les DVE ?

a) Au bloc opératoire

b) En réanimation

c) Au bloc opératoire et en réanimation

10) Utilisez-vous une antibioprophylaxie lors de la pose de DVE ?

a) Jamais

b) Parfois (< 50% des cas)

c) Souvent (> 50% des cas)

d) Systématiquement

11) A quelle fréquence programmez-vous le changement de la tubulure et du système collecteur ?

a) Plusieurs fois par semaine

b) Une fois par semaine

c) Toutes les 2 semaines

a) Vous ne pratiquez pas de changement systématique

12) Comment protégez-vous le robinet proximal de la DVE ?

a) Sous la capeline

b) Dans une compresse ou pansement américain

c) Dans une compresse imbibée d'antiseptique

d) Dans un boîtier

e) A l'air libre

13) Les DVE sont-elles systématiquement mises en culture après leur retrait (hors contexte d'infection) ?

a) Oui

b) Non

13bis) Si la culture du cathéter de DVE revient positive

(Ne pas répondre si vous avez répondu « non » à la question précédente)

a) Vous considérez d'emblée qu'il s'agit d'une infection

b) Vous considérez l'analyse du LCS et l'état clinique pour différencier infection et colonisation/contamination

b) Vous pratiquez une analyse de LCS systématiquement

c) Vous débutez une antibiothérapie d'emblée

d) Vous débutez une antibiothérapie d'emblée uniquement pour certains germes

e) Vous débutez une antibiothérapie uniquement si l'analyse du LCS et l'état clinique font suspecter une infection

f) Si une dérivation ventriculaire interne a été posé, il faut la retirer systématiquement

14) Utilisez-vous des cathéters de DVE imprégnés d'anti infectieux ?

a) Jamais

b) Parfois (< 50% des cas)

c) Souvent (> 50% des cas)

d) Systématiquement

14bis) Vous utilisez des cathéters de DVE imprégnés d'anti infectieux

(Ne pas répondre si vous avez répondu « jamais » à la question précédente)

a) En première intention

b) Seulement lors d'un changement pour infection de DVE

15) Au sein de votre unité, les cathéters de DVE sont-ils tunnélisés sous la peau ?

a) Jamais

b) Parfois (< 50% des cas)

c) Souvent (> 50% des cas)

d) Systématiquement

15bis) Quelle distance de trajet tunnélisé pratiquez-vous ?

(Ne pas répondre si vous avez répondu « jamais » à la question précédente)

a) < 5cm

a) > 5cm

Prise en charge d'une infection / colonisation sur DVE

16) Vous suspectez une COLONISATION de DVE, quelle est votre prise en charge ?

a) Confirmation systématique par un nouveau prélèvement de LCS sur le robinet de la ligne patient (proximal)

b) Changement du circuit externe en première intention, puis réalisation de nouveaux prélèvements

c) Changement de la DVE en première intention

d) Introduction d'une antibiothérapie

17) Vous suspectez une INFECTION sur DVE, quelle est votre prise en charge ?

a) Confirmation systématique par un nouveau prélèvement de LCS sur le robinet proximal

b) Changement de la DVE en urgence

c) Changement de la DVE après 48-72h d'antibiothérapie

d) Changement de la DVE après négativation des cultures

e) pas de changement de DVE

18) En cas de suspicion d'infection sur DVE, quelle association d'antibiotiques probabilistes intra-veineux utilisez-vous en première intention ?

Anti BGN

a) Cefotaxime

b) Ceftriaxone

b) Cefepime

c) Ceftazidime

d) Meropenem

Anti Staphylocoque

e) Vancomycine

f) Linezolide

g) Fluoroquinolone

h) Fosfomycine

i) Autres

19) En cas d'infection à Staphylocoque sensible à la Méticilline, quelle antibiothérapie intra-veineuse utilisez-vous en première intention ?

a) Oxacilline

b) Cefotaxime

c) Ceftriaxone

d) Cefazoline

e) Bactrim

f) Fluoroquinolone

g) Association Bactrim-Rifampicine

h) Association Fluoroquinolone-Rifampicine

i) Autres

20) En cas d'infection à Staphylocoque résistant à la Méticilline, quelle antibiothérapie intra-veineuse utilisez-vous en première intention ?

a) Vancomycine

b) Linezolide

c) Daptomycine

d) Ceftaroline

e) Autres

21) Quelle est la durée de l'antibiothérapie intra-veineuse en fonction du germe ?

	7j	14j	21j	>21j
Staph Aureus				
Staph Coag Neg				
Bacille Gram Neg				
P Acnes				
P Aeruginosa				

22) Réalisez-vous des dosages dans le LCS d'antibiotiques utilisés par voie systémique ?

a) Jamais

b) Parfois (< 50% des cas)

c) Souvent (> 50% des cas)

d) Systématiquement

23) En cas d'infection avérée, comment monitorez-vous la réponse au traitement antibiotique ?

a) Surveillance clinique

b) Surveillance des marqueurs sanguins (leucocytes, CRP, PCT)

c) Prélèvement de LCS systématique

d) Prélèvement de LCS seulement si mauvaise évolution clinique

e) Prélèvements de LCS répétés jusqu'à négativation des cultures

24) En cas d'infection avérée, quel délai retenez-vous avant de poser une dérivation ventriculaire interne si nécessaire ?

a) 48h d'antibiothérapie

b) 2 à 7j d'antibiothérapie

c) 48h après la négativation des cultures

d) 2 à 7j après la négativation des cultures

e) Plus de 7j après la négativation des cultures

e) Le délai dépend du germe

f) Le délai est basé sur la protéinorachie

Antibiothérapie intra ventriculaire

25) Dans quels cas utilisez-vous une antibiothérapie intra-ventriculaire ?

a) Jamais

b) Si échec de l'antibiothérapie intra-veineuse seule

c) Si le germe est résistant

d) En cas de ventriculite à l'imagerie

e) En cas d'abcès à l'imagerie

f) Systématiquement

g) Autres

26) Si vous réalisez une antibiothérapie par voie intra-ventriculaire, pratiquez-vous le dosage des antibiotiques dans le LCS avant réinjection ?

a) Jamais

b) Parfois (< 50% des cas)

c) Souvent (> 50% des cas)

d) Systématiquement

27) Après l'injection d'antibiotique intra-ventriculaire, combien de temps clampez-vous la DVE ?

a) Pas de clampage

b) Clampage moins de 15 minutes

c) Clampage entre 15 et 60 minutes

d) Clampage plus de 60 minutes

28) Comment adaptez-vous la dose d'antibiotique intra-ventriculaire ?

a) Dose standard identique pour tous les patients

b) Adaptation de la dose par rapport au volume ventriculaire à l'imagerie

c) Adaptation de la dose selon le germe isolé

d) Adaptation de la dose par rapport à la CMI

e) Adaptation de la dose en fonction du dosage de l'antibiotique dans le LCS

29) Quelle fréquence d'administration de l'antibiothérapie intra-ventriculaire ?

a) Quotidienne

b) 1 jour sur 2

c) 1 jour sur 3

d) Adaptation en fonction de la quantité de LCS drainé

e) Adaptation de la dose en fonction du dosage de l'antibiotique dans le LCS

30) Quelle durée pour l'antibiothérapie intra-ventriculaire ?

a) Dose unique

b) Moins de 3 jours

c) 3 à 7 jours

d) plus de 7 jours

e) Jusqu'à arrêt de l'antibiothérapie intra-veineuse

f) Adaptation de la durée selon le germe isolé

Supplemental data 2 : Review article

Management of EVD

EVD management has a decisive impact on VRI prevention. This management has improved significantly over the last 20 years, which led to a decrease in the rate of VRIs (18.3 per 1000 catheter days before the 2000s, to 10.5 per 1000 catheter days after the 2000s) (1).

Place of insertion

In our study, the vast majority of centers place their EVDs in the operating room. Most studies (2–5) did not find an association between the location of EVDs placement (operating room or ICU) and the rate of VRI. However, Clark et al. (4) found a higher rate of subdural empyema, bone flap infection and brain abscess for EVDs placed in ICU. Some studies (1,6,7) find that VRI occur mainly in the days following the placement of EVDs, which suggests that most VRI might be due to aseptic errors during the placement of EVDs. By instituting a protocol for sterile placement of EVDs, Riverside Methodist Hospital in Ohio (8) has drastically reduced its number of VRI (from 16 to 3.2 VRI per 1000 EVD catheter days). In view of current knowledge, it seems reasonable not to prohibit the placement of EVDs in ICU, but rigourous hygienic measures must be applied, and it is probably useful to adopt a protocol for the placement of EVDs (8–11).

Antibioprophylaxis

The use of antibiotic prophylaxis during EVD placement has been a long debated topic. The US recommendations (12) recommend antibiotic prophylaxis, whereas the French recommendations (13) recommend no prophylaxis.

In this study it appears that there is no consensus among our participants on the subject of antibiotic prophylaxis, 61% of them do not use antibiotic prophylaxis according to French recommendations.

Blomstedt et al. and Djiandjian et al. (14,15) showed a decrease in the rate of VRI with the use of antibiotic prophylaxis. Most other studies on the subject (2–4,6,16–26) do not find a significant difference, but this might be due to a lack of power. Three meta-analyses (27–29) based only on randomized controlled studies show a decrease in VRI rate with antibiotic prophylaxis with an odd ratio of 0.52. In these studies, all antibiotic therapies target methicillin susceptible Staphylococcus Aureus and only 20% target gram-negative bacteria (GNB) (29), but 35% of VRI are due to GNB (1). It should be noted that the use of antibiotic prophylaxis may favor VRI with resistant germs (MRSA, Serratia) or opportunistic germs (Candida species) (30,31).

Anti-infectives impregnated catheter

The majority of participants in our study never use an anti-infective impregnated EVD catheter.

However, a number of studies (32–39), including a good quality randomized controlled trial by Zabramski et al. (40), indicate that the use of an anti-infective-impregnated EVD catheter reduces the rate of VRI. Several meta-analyses (1,29,41,42) conclude a reduction in VRI with an odd ratio between 0.19 and 0.37. In most of the studies, the catheters are impregnated with Clindamycin associated with Rifampicin, which confers them an activity against staphylococci. Thus, there is a major decrease in staphylococcal VRI in patients treated with EVDs impregnated with Clindamycin and Rifampicin (1,32,33), Harrop et al. (34) found a decrease in staphylococcal VRI from 6.1% to 0.2%. From in vitro studies, it is known that these catheters can have a very prolonged antibacterial action, up to 127 days (43).

However, the in vitro study by Stevens et al. (44) suggested that CSF samples collected through an antibiotic-impregnated EVD may be biased and lead to false-negatives, and therefore undertreatment of patients.

EVD tunneling

Tunneling of EVD catheters was proposed by Friedman in 1980 (45), in an attempt to reduce catheter contamination by skin flora.

There are no randomized studies on the subject, and the existing studies have low levels of evidence but indicate decreases in VRI and a decrease in the accidental removal of EVDs (46,47).

The length of the tunneling may have an impact on the rate of VRI; Omar et al. (48) found a large decrease in VRI in patients with tunnelings longer than 5 cm compared with tunnelings shorter than 5 cm (odd ratio 0.18). Some authors have tried lengths of more than 40cm but without satisfying results (49).

Tubing and collection system changes

In an attempt to decrease the number of VRI, some authors have tried to change the EVD catheter systematically and regularly, but this practice had the opposite effect, increasing the number of VRI (50). Routine and regular change of the EVD tubing and collecting system has not been tested in any study, however, it is known that increased handling and opening of the closed system causes an increase in VRI (10,51,52). Therefore, it does not seem reasonable to practice systematic and regular replacement of the EVD tubing and the collection system.

Protection of the proximal valve

The proximal tap of the EVD allows for CSF collection and antibiotic injection, but it is an entry point for germs and its manipulation results in a large increase in VRI (51). Implementing service protocols for EVD management and nursing significantly reduces VRI (8–11). In our study 73.5% of participants implement a measure to protect the proximal tap from infection.

Diagnosis of VRI

Definition of VRI

Making the diagnosis of VRI is often difficult because neurosurgery, head trauma, or intracranial bleeding can also cause clinical signs (cephalalgia, meningeal stiffness, fever) and CSF changes (53). The definition used for the diagnosis of VRI will have a major impact on the management of the patient ; an underdiagnosis leads to a delay in treatment, which is clearly negative to the prognosis (54). On the other hand, antibiotic therapy for aseptic meningitis is detrimental to the patient and leads to the development of resistant germs (55).

Ramanan et al (1) performed a meta analysis of 35 studies, and found a rate of reported VRI highly correlated with the definition of VRI used. Using the Centers for Disease Control definition (56,57) the average VRI rate is 8.8/1000 catheter-days. But 50% of the studies define VRI only by a positive culture, which leads to an overdiagnosis (VRI rate in these studies at 11.5/1000 catheter-days) because colonization and contamination are also included. The broadest definitions are : a positive culture or a change in clinical status or a change in CSF, which leads to excessively high VRI rates of 17%. The great heterogeneity in the definitions of VRI makes it difficult to compare the studies between them.

In order to help find a consensual definition, Lozier et al. (53) suggested a diagnostic method that differentiates contamination, colonization, ventriculostomy related infection and ventriculitis. They proposed the following criteria for the diagnosis of VRI : a positive CSF culture or Gram's stain, associated with LCS changes (progressively declining CSF glucose and increasing CSF protein profiles accompanied by advancing CSF pleocytosis), and clinical symptoms other than fever.

The 2017 US recommendation (12) provides a diagnostic method that is very similar to Lozier et al.

Lactate

A minority of participants in our study use the CSF lactate assay to aid in the diagnosis of VRI.

However recent large meta-analyses (58,59) found a sensitivity of 93-97% and a specificity of 94-96%, with a better ROC curve than conventional markers (CSF glucose, CSF/plasma glucose quotient, CSF protein, and CSF total number of leukocytes). The sensitivity seems to be excellent, but there is a great heterogeneity in the specificity depending on the studies (from 43 to 100%) (58). This is due to the fact that lactate can be increased for other reasons : subarachnoid hemorrhage (37), recent stroke (60), seizure (61), brain trauma (62), hypoglycemia (63), sedation withdrawal (64). When studying the diagnostic value of lactate with patients with EVD, the specificity is not as good (Wong et al. found a positive predictive value of only 60%, and a negative predictive value of 100% with a lactate cutoff of 4mmol/L) (65).

Another interesting point is that the rapid decrease of lactate at the initiation of treatment (more than 50% during the first 3 days) might a good prognostic marker (66).

PCT

Plasma PCT is a good marker of bacterial infection (67), very early (elevation from the 4th hour) (68), which does not increase in inflammation of non-infectious origin (69).

In case of meningitis, PCT seems to have a very good specificity but a low sensitivity (Schwartz et al. find a specificity of 100%, better than the leukocyte count or the lactate level in the CSF) (70), the low sensitivity could be explained by the fact that the infection is localized and with a low systemic impact. Studies on the diagnostic value of plasma PCT in VRI are few in number, with very small patient samples and are discordant between them (71–73) ; there are no randomized studies. For the moment, the evidence for the usefulness of PCT in the diagnosis of VRI is weak.

Cell index

The cell index was defined in 2004 by Pfausler et al (74) by the formula (CSF leukocyte / CSF erythrocyte) / (blood leukocyte / blood erythrocyte). In this study, the cell index allows the diagnosis of VRI up to 3 days before culture positivity, it is not the absolute value of the cell index that is important but its variation over time. This study has a very small number of patients, methodological biases and an abnormally high rate of VRI; moreover, this method requires daily CSF sampling in order to observe the variation of the cell index over time, which increases the handling of EVD and therefore the rate of VRI (10,51,52). The study by Schade et al (75), with a much larger number of participants, did not confirm the usefulness of the cell index.

Therefore, the cell index cannot be recommended based on the current data. In our study, the majority of participants used the cell-index for the diagnosis of VRI, which may seem surprising given the low level of evidence on this marker.

16S RNA PCR

There are a few studies on the broad-range 16S rRNA PCR for the diagnosis of VRI. Banks et al. (76) found excellent sensitivity (no CSF samples with positive culture and negative PCR). However, 49% of CSF samples had a negative culture and a positive PCR, which may be due to false positive PCRs or samples with a false negative culture (due to antibiotics for example (77)). Another study (78) found contradictory results with a sensitivity of only 47% and a good specificity of 93%.

A great advantage of PCR is that it allows very fast results, which can be useful with some germs of difficult or slow culture (Propionibacterium Acnes or some GNB). PCR probably has real utility in the diagnosis of VRI but needs more study before recommending its use.

Brain imaging

In case of suspected VRI, imaging is used to diagnose ventriculitis and to look for complications (brain abscess, subdural empyema, hydrocephalus, thrombosis) (79,80). Imaging allows for early diagnosis, which reduces the number of complications and mortality (81,82). Only 1/3 of the participants in our study do imaging systematically

CT is more easily performed but magnetic resonance imaging is more sensitive for detecting ventriculitis (81,83). CT requires the use of contrast medium to diagnose ventriculitis (ependymal enhancement), noncontrast CT scanning may be normal in case of ventriculitis (84). MRI may be contraindicated with some EVD catheters that contain metal; the most interesting sequences are FLAIR (85), diffusion-weighted imaging and T1 weight post-contrast images (86).

Today, all neuro ICUs in the ANARLF network have access to MRI, however in our study the vast majority of participants perform CT as first line, this is probably due to the fact that this imaging is more easily and quickly available.

Management of VRI

Antibiotherapy

In older studies (25), it seems that VRI was caused mainly by germs of the cutaneous flora, however we observe an increase in the proportion of VRI caused by GNB (26,87). In a recent meta-analysis of 35 studies (1), the most frequent bacteria in VRI are Staphylococci which represent 54% of cases (coagulation-negative Staphylococci 38%, MSSA 12.4%, MRSA 2.3%), followed by gram-negative bacteria at 35% (Acinetobacter species 9%, Enterobacter species 6%, Pseudomonas Aeruginosa 6%, Klebsiella species 3%, E Coli 2%, Serratia Marcescens 2%). It is notable that the most frequent GNB (Acinetobacter species, Enterobacter species and Pseudomonas Aeruginosa) are more resistant germs than the other enterobacterias.

However, the bacterial ecology is different from one country to another, for example the most frequent germs in Europe are coagulation-negative Staphylococci (10,25,88,89), while in the United States the most frequent germs in some studies are GNB (2,87). Thus, it is necessary to take into account the local bacterial ecology to start a probabilistic antibiotic therapy.

There are very few controlled clinical trials on antibiotic strategy in VRI, most recommendations are based on small observational clinical trials.

In cases of meningitis, it appears that antibiotic treatment should be started promptly. Delayed management increases the rate of death (90) and the rate of neurological sequelae (91).

In our study, almost all participants used a bi-antibiotic therapy in case of VRI, including an anti-staphylococcal antibiotic (mainly Linezolid or Vancomycin) and an antibiotic effective against gram-negative bacteria (mainly Meropenem, Cefotaxime, Ceftazidime or Cefepime).

Regarding the gram-negative antibiotic, the majority of participants chose an antibiotic effective against Pseudomonas Aeruginosa (Meropenem, Ceftazidime, or Cefepime), which is also recommended by the Infectious Diseases Society of America (12). Both Ceftazidim and Cefepime have modest meningeal penetrations (92,93), but appear to be effective in Pseudomonas Aeruginosa meningitis (94–96). It should be noted that both antibiotics can have neurological side effects (confusion, myoclonus and seizure) (97). However, about 30% of the participants preferred to use Cefotaxime or Ceftriaxone to target GNB. This may be explained by the bacterial ecology of their ward with low levels of Pseudomonas Aeruginosa. These two antibiotics have a modest distribution in the CSF (98–101), but have been shown to be effective against GNB meningitis (102,103).

There is an increase in the rate of VRI with multi-resistant gram-negative bacteria. The most common is Acinetobacter species (1) which accounts for 9% of VRI, with an increasing incidence (104) and has become the most common germ in some countries (26,105). The probabilistic antibiotic therapy recommended by the Infectious Diseases Society of America (12) is Vancomycin

combined with Cefepime or Ceftazidime or Carbapenem. The problem is that using Cefepime or Ceftazidime only treats 10% of Acinetobacter (93), due to antibiotic resistance (106). It is therefore essential to know the bacterial ecology of the department before prescribing probabilistic antibiotic therapy.

Carbapenems have modest meningeal penetration (107) but appear to be effective in cases of VRI with Acinetobacter species (108–111) or Cephalosporin-resistant Pneumococci (111–114). Meropenem causes less seizure than Imipenem (115,116). For optimal efficacy, slow injection or continuous injection with an electric syringe pump is preferred (117,118). It is important to note the existence of Acinetobacter resistant to Carbapenem, which represent 55% of cases (93,119), we see the appearance of Acinetobacter resistant to almost all antibiotics (120). The mortality rate of Acinetobacter VRI is about 15% (93), but can increase to 71% in cases of local Carbapenem-resistant Acinetobacter ecology (121).

The Infectious Diseases Society of America (12) recommends treating Acinetobacter Baumannii with intravenous Meropenem. It appears that the addition of intravenous aminoglycoside may increase the cure rate (79% cure rate reported by Kim et al.) (93). In cases of Carbapenem-resistant Acinetobacter, treatment with Colistin or Polymyxin B is recommended (12). This treatment looks effective intraventricularly (122), or combined intravenous and intraventricularly (123,124), but does not seem to be indicated intravenously alone (93). It should be noted that the neurological toxicity of Colistin or Polymyxin B is frequent (meningeal irritation) but reversible (122).

For Methicillin-sensitive Staphylococcus VRI, the most commonly used antibiotic by our participants is Cloxacillin, which is also the antibiotic recommended by Infectious Diseases Society of America (12).

About 20% of our participants use a combination of antibiotics including Rifampicin. Rifampicin has excellent penetration into CSF, even in the absence of meningeal inflammation (125,126), and has good penetration into bacterial biofilms that may form on contact with materials (127). On Rifampicin-susceptible Staphylococci, this antibiotic seems to be effective (128), but should never be

used as monotherapy to avoid the development of resistance (129). Rifampicin is very useful in case of infection of equipment, especially if it is impossible to remove it (12).

Concerning Methicillin-resistant Staphylococci, the Infectious Diseases Society of America (12) strongly recommends the use of Vancomycin as a first-line treatment, but in our study, the majority of participants preferred to use Linezolid.

This non-use of Vancomycin can be explained by several reasons. The first reason is its complexity of use, as it requires regular dosing to be sure of the efficacy, an underdosing of Vancomycin leads to treatment failures (130). It seems that the target blood level of Vancomycin is 15-20 µg/mL (129,131). Another reason is the risk of adverse effects in patients with organ dysfunction. Another problem with Vancomycin is its poor penetration into the CSF, which can sometimes be insufficient in cases of moderate meningeal inflammation (132).

In contrast to Vancomycin, Linezolid is simpler to use and has an excellent penetration in the CSF close to 80% (133). Many articles show the efficacy of Linezolid in case of VRI with Methicillin-resistant Staphylococcus (134–142).

Daptomycin and Trimethoprim-Sulfamethoxazole are also options in case of contraindication to Vancomycin (12,143).

Duration of antibiotic therapy

There are no randomized controlled trials comparing duration of antibiotic therapy in care-related meningitis.

In his prospective multicenter study, Kestle et al (144) found a 26% rate of reinfection after antibiotic treatment. Antibiotic duration ranged from 4 to 47 days, but this duration did not correlate with the rate of reinfection (mean antibiotic duration in the "reinfection" group was 17.4 days, it was 16.2 days in the "no reinfection" group). These data are confirmed by the study by Simon et al (145), which also found a reinfection rate of 26%, and no correlation between duration of antibiotic therapy and reinfection rate.

The Infectious Diseases Society of America (12) recommends an antibiotic duration of 10-14 days (possibly up to 21 days for some GNB). If cultures remain positive despite antibiotics, the Infectious Diseases Society of America recommends maintaining 10-14 days of antibiotics after the last positive culture.

Intraventricular antibiotic therapy

An intravenous antibiotic must cross the blood-brain barrier to reach the CSF, the passage of this barrier depends on the lipophilicity of the antibiotic, its molecular weight and its protein binding (146). Some hydrophilic antibiotics (Glycopeptides, Aminoglycosides) therefore have a very poor penetration in the CSF (146). This penetration is correlated to the level of meningeal inflammation, it can be improved in case of VRI (147) and decreased in case of use of corticoids (148). Vancomycin is known to have poor penetration into the CSF (149–151), Caricato et al (152) showed with a cerebral microdialysis method that concentrations of vancomycin administered intravenously (25 mg/kg/day) in the edematous brain were never higher than the minimal inhibitory concentrations. Similarly Aminoglycosides do not cross the blood-brain barrier (52), they have a penetration rate in the CSF < 1% (153,154).

A major advantage of intraventricular antibiotic therapy is that it shunts the blood-brain barrier, so we are in a one-compartment system (155) which simplifies the pharmacokinetic model. It allows to have appropriate antibiotic concentration in CSF, without having massive blood concentration, which can decrease systemic adverse effects of antibiotics (149,150,156).

The indications for intraventricular antibiotic therapy are not consensual, some authors recommend it in case of failure of intravenous antibiotic therapy (12,148), in case of impossibility to remove infected material (12,148), in case of ventriculitis (151), in case of infection with a highly resistant germ (148), in case of inability to achieve antibiotic concentration in the CSF with non-toxic doses of antibiotic (155).

There are no intraventricular antibiotics approved by the US Food and Drug Administration. However, the use of intraventricular antibiotics could increase in the coming years due to the proliferation of multi-resistant germs (93,119,120).

Regarding intraventricular antibiotic therapy, there is only one randomized study in adults on a very small sample (132), very few prospective studies, current recommendations are mainly based on expert opinion (12,157). Most studies show faster CSF sterilization using a combination of intraventricular and intravenous antibiotics than intravenous alone (155,158). Wilki et al. (158) also showed a decrease in total systemic antibiotic duration and a decrease in hospitalization time. The two most commonly used intraventricular antibiotics are Vancomycin and Gentamicin (93,132,149,155,157).

Several studies show good efficacy of intraventricular Vancomycin (151,159,160), and optimal CSF concentration even 24 hours after injection (161). Pfausler et al (132) did a randomized study on 10 patients to test intravenous Vancomycin alone versus intra ventricular alone, in the group with intravenous Vancomycin the antibiotic dosage in the CSF is never above the MIC, while in the intra ventricular Vancomycin group the dosage is optimal during the 21 hours after injection.

Similarly, the addition of intraventricular Gentamicin to intravenous antibiotic therapy shows good results (162,163), decreased mortality (164), and decreased recurrence rate of GNB infections (163). Studies are less common on Amikacin, but it seems that this antibiotic is effective by intra ventricular route (165), it may have a better effectiveness against some resistant germs like Acinetobacter species (166).

Colistin has also shown intraventricular efficacy in multi-resistant gram-negative bacteria (93,122–124,149,155,162,167). There are also a few case reports of treatment of Methicillin-resistant Staphylococci with intraventricular Daptomycin (168–171). On the other hand, penicillins, cephalosporins and Carbapenems should not be injected intraventricularly

because of neurological side effects (confusion, encephalopathy, myoclonus and epileptic seizures) (149,172,173).

There is no consensus regarding the dose of intraventricular antibiotic, for example for Vancomycin the doses range from 0.075 (174) to 50mg/day (175) depending on the articles, with the most evidence for doses of 5 to 20mg/day (151). It is difficult to determine an optimal dose, because pharmacological studies show very variable results depending on the patient (151,155,158,159,162,163,167,176,177). It is probable that the best solution is to adapt the antibiotic dose to each patient.

The antibiotic dose should also be adjusted to the minimum inhibitory concentration (146,178). It is probably useful to perform antibiotic assays in CSF, as the antibiotic concentration should be greater than 10 to 20 times the MIC (146,151,178).

The antibiotic dose probably needs to be adjusted to the volume of distribution, i.e., the ventricular volumes (151). Ventricular volumes in adults are about 150-250mL (177,179), but may increase in cases of hydrocephalus or intraventricular hemorrhage (Lebret et al. (180) found ventricles of 590mL in patients with hydrocephalus), or decreased in case of CSF drainage by EVD or by decreased CSF production by the choroids plexuses in case of infection (181) (Hirsch et al. (182) found ventricles of 60mL). The British Society for Antimicrobial Chemotherapy (157) recommends estimating the volume of the ventricles on imaging to allow adjustment of the antibiotic dose (5mg of Vancomycin if the ventricles are small, 10mg if they are of normal size, 15-20mg if they are large).

Regarding the frequency of intraventricular antibiotic injection, most studies performed one injection per day (151). However, the half-life of the antibiotic is highly unpredictable, with wide inter- and intra-patient variation during treatment (132,161,175). It is probably useful to perform antibiotic assays in order to adapt the injection frequency (151). The volume of CSF drained by the EVD has a strong impact on the clearance of the antibiotic (151), the British Society for Antimicrobial Chemotherapy (157) recommends adapting the

frequency of injections to the rate of CSF drainage (2 injections of antibiotic per day if the CSF drainage is greater than 200mL/day, 1 dose per day if CSF drainage is greater than 100mL/day, 1 dose every 2 days if CSF drainage is between 50 and 100mL/day, 1 dose every 3 days if CSF drainage is less than 50mL/day).

Regarding EVD clamping time after antibiotic injection, most studies perform clamping between 15 and 60 minutes (177), which is recommended by the Infectious Diseases Society of America (12), the British Society for Antimicrobial Chemotherapy (157) recommends 15 minute clamping.

The duration of intraventricular antibiotic therapy is highly heterogeneous according to studies, ranging from 7 to 21 days (151). The British Society for Antimicrobial Chemotherapy (157) recommends 5 to 7 days, but this is based on expert opinion only. Some authors recommend continuing intraventricular antibiotics for 48-72 hours after CSF sterilization (155). Other authors recommend waiting for improvement in clinical status, CSF parameters, and CSF sterilization before stopping the intraventricular antibiotic (151).

Most studies suggest that intrathecal administration of colistin, aminoglycosides and vancomycin is not associated with severe or irreversible toxicity (132,151,155,159,161,183,184). Toxicity appeared to be dose related (183), the rare adverse effects referenced for intraventricular Vancomycin are hearing loss, ataxia, headache, red man syndrome (183), and for Gentamicin are temporary hearing loss, epilepsy (183) and reversible polyradiculitis (185).

It should be noted that a meta-analysis (176) based on a single study found an increase in mortality (relative risk of 3.4) when intraventricular antibiotics were used in neonates. It is probably not advisable to use this treatment in newborns. Studies conducted in older children (0-15 years) do not show this increase in mortality (186).

In conclusion, intraventricular antibiotic therapy appears to be effective, but due to the lack of evidence it should probably not be used routinely and should be reserved for selected patients.

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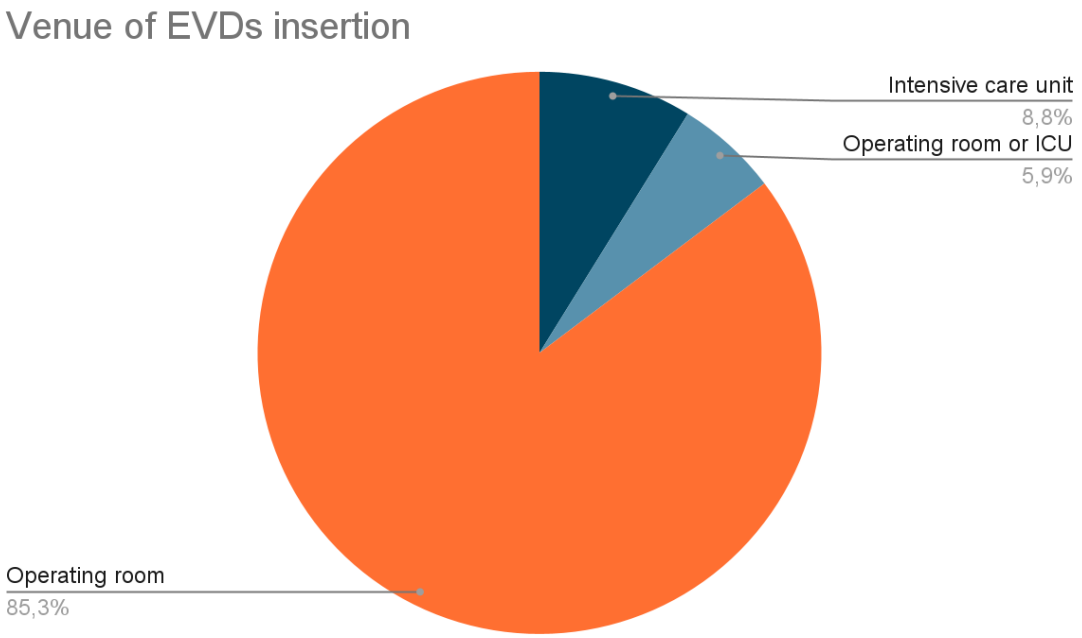
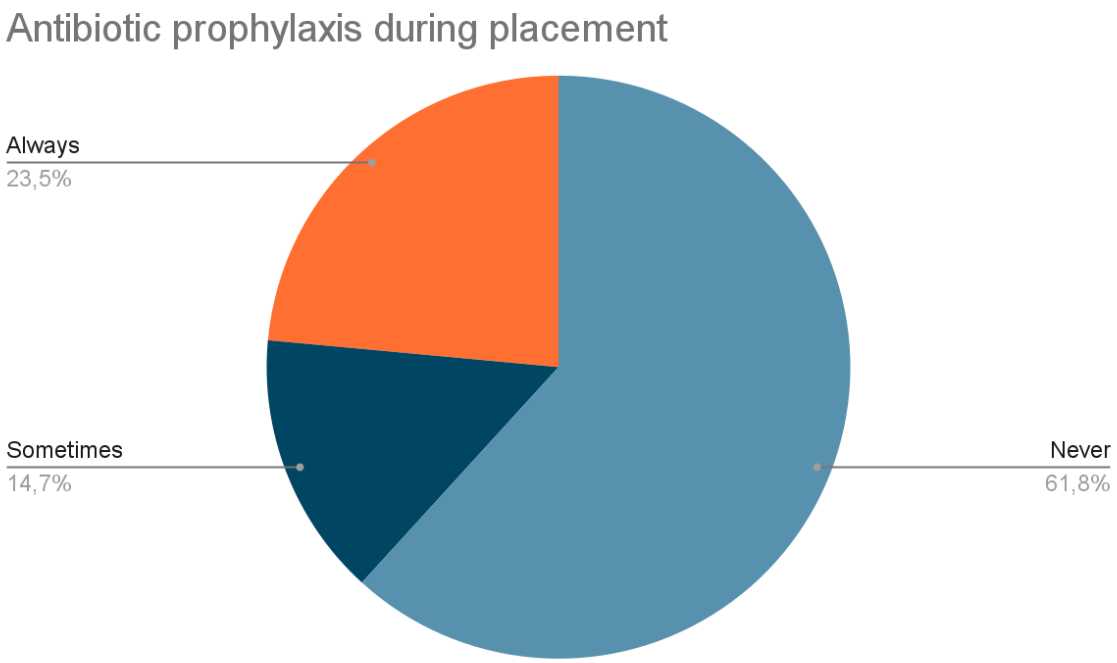
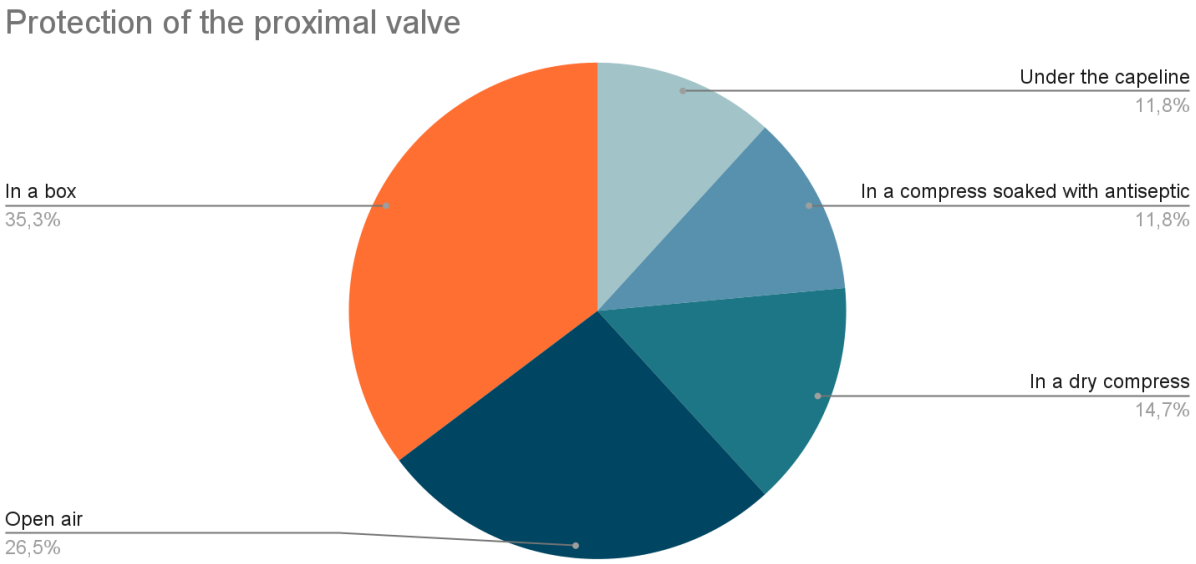
Supplemental data 3 : Figures

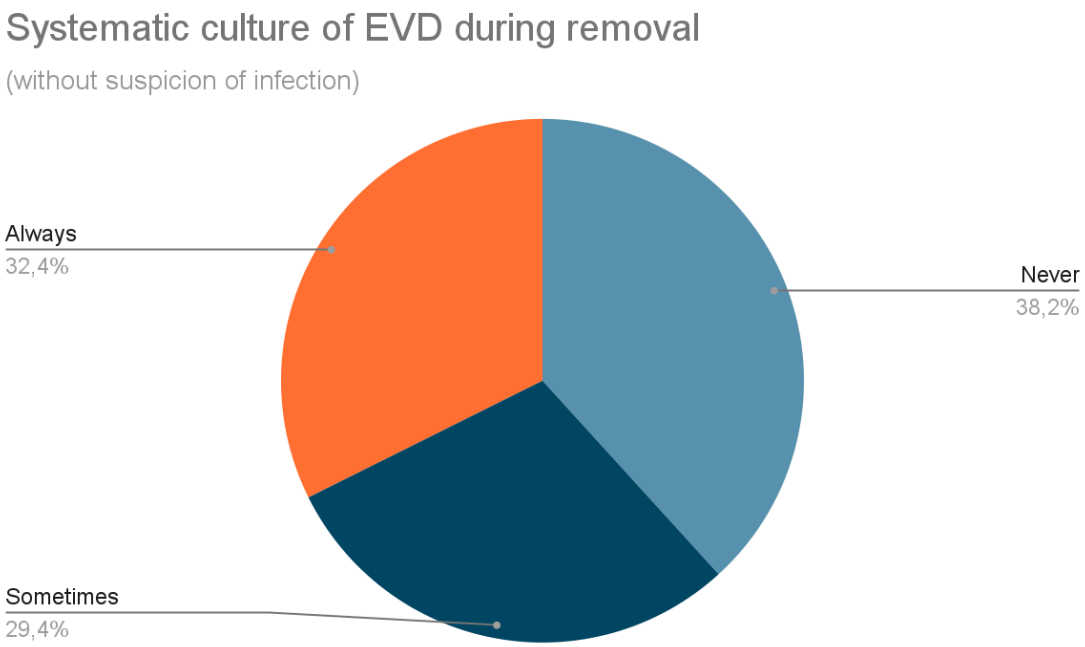
	Never	Less than 50% of cases	More than 50% of cases	Always
Use of antibiotic prophylaxis during DVE placement	61,8 %	11,8 %	2,9 %	23,5 %
Use of EVD impregnated with anti-infectives	79,4 %	14,7 %	-	5,9 %
EVD tunneling	17,6 %	-	8,8 %	73,5 %
Systematic culture of EVD during removal	38,2 %	23,5 %	5,9 %	32,5 %
Performing of 16S RNA PCR for the diagnosis of VRI	20,6 %	67,6 %	11,8 %	-
Brain imaging in the case of VRI	5,9 %	32,4 %	35,3 %	26,5 %
Antibiotic dosages in CSF in case of intravenous antibiotic therapy	26,5 %	38,2 %	23,5 %	11,8 %
Antibiotic dosages in CSF in case of intraventricular antibiotic therapy	43,3 %	40 %	16,7 %	-

	No	Yes
Use of CSF lactate level for the diagnosis of VRI	61,8 %	38,2 %
Use of blood procalcitonin level for the diagnosis of VRI	82,4 %	17,6 %
Use of the cell index for the diagnosis of VRI	32,4 %	67,6 %

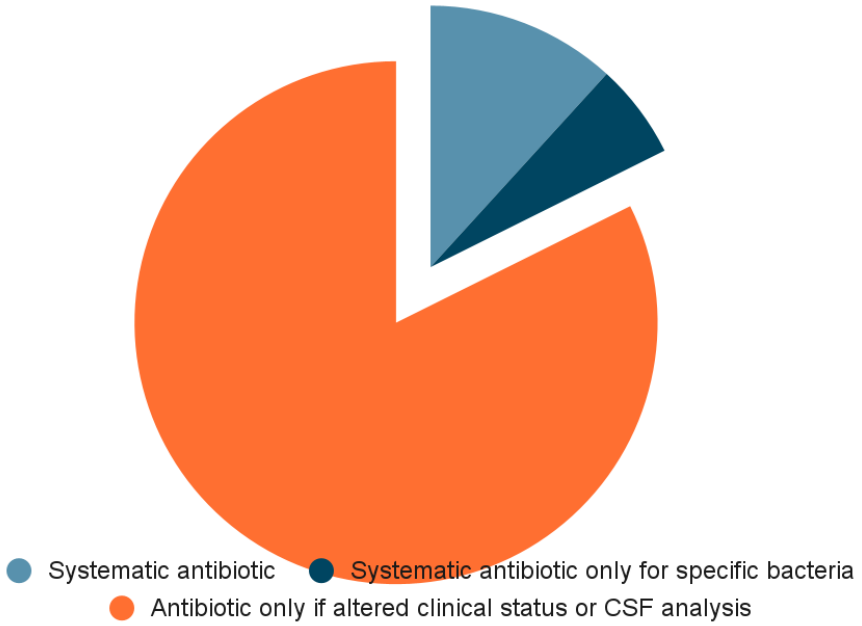

Venue of EVDs insertion
Intensive care unit
8,8%
Operating room or ICU
5,9%
Operating room
85,3%


Antibiotic prophylaxis during placement
Always
23,5%
Sometimes
14,7%
Never
61,8%

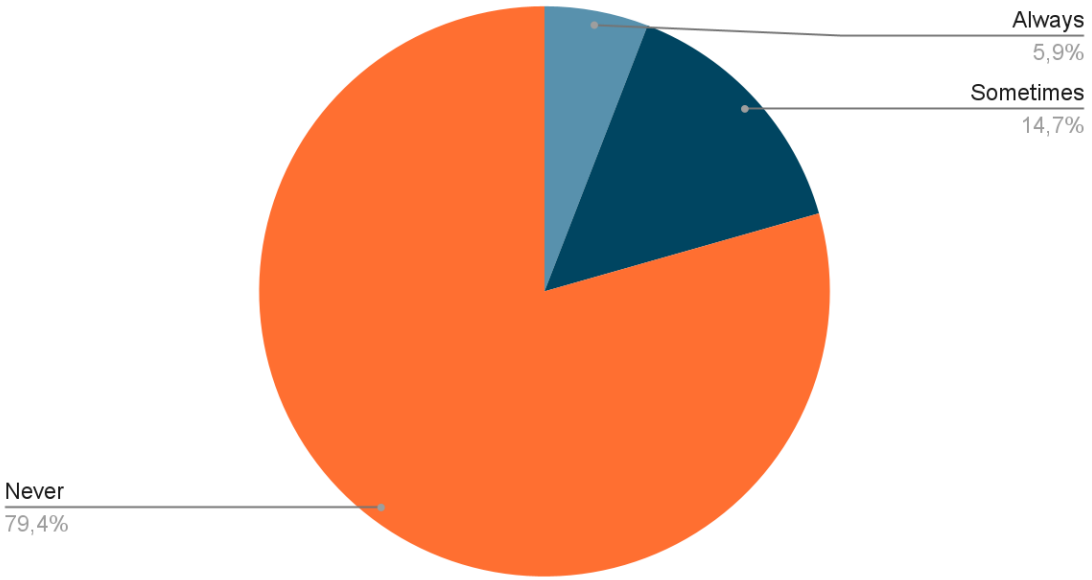

Protection of the proximal valve
Under the capeline
11,8%
In a compress soaked with antiseptic
11,8%
In a dry compress
14,7%
Open air
26,5%
In a box
35,3%


Systematic culture of EVD during removal
(without suspicion of infection)
Never
38,2%
Sometimes
29,4%
Always
32,4%

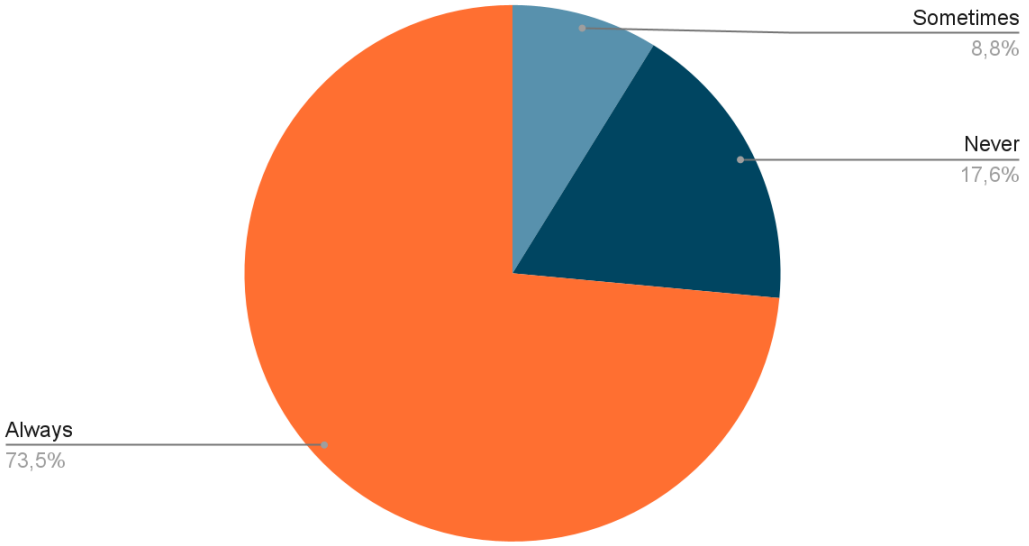
Management of a positive EVD culture, sent systematically without suspicion of infection



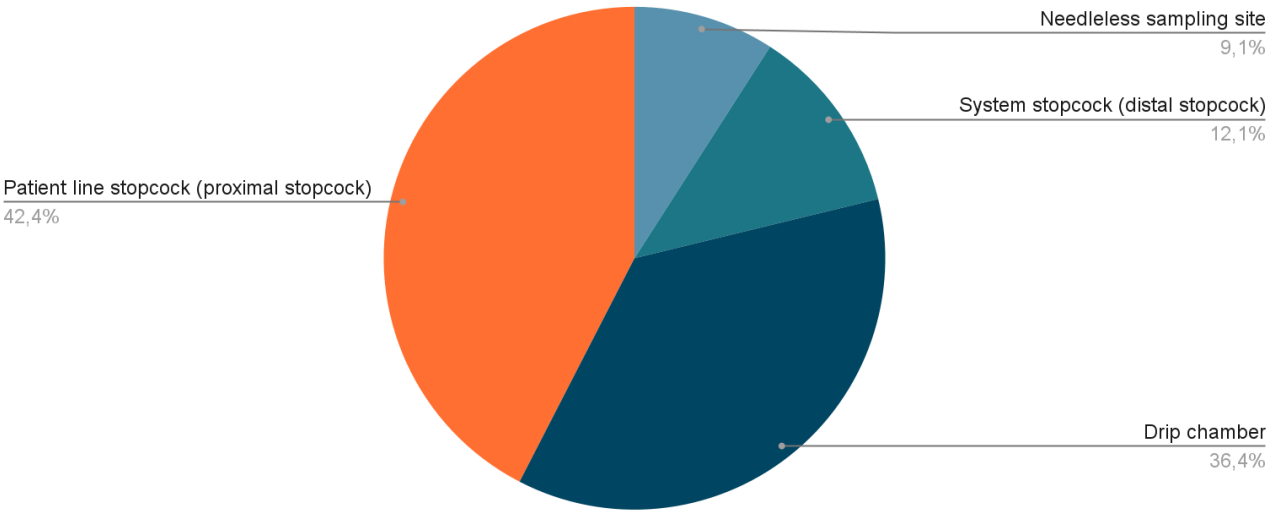
EVD impregnated with anti-infectives

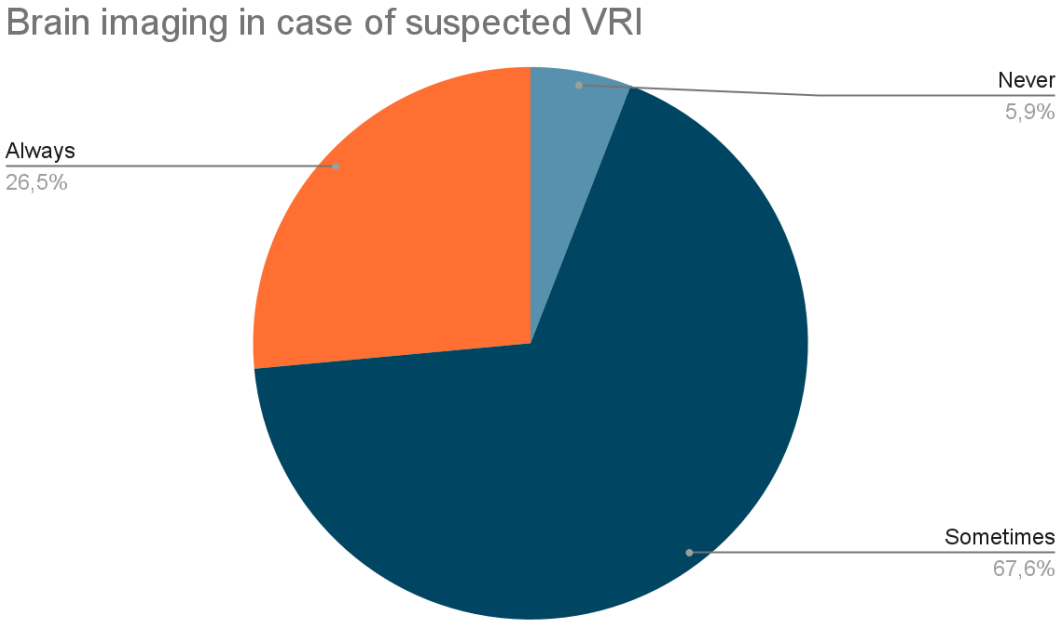


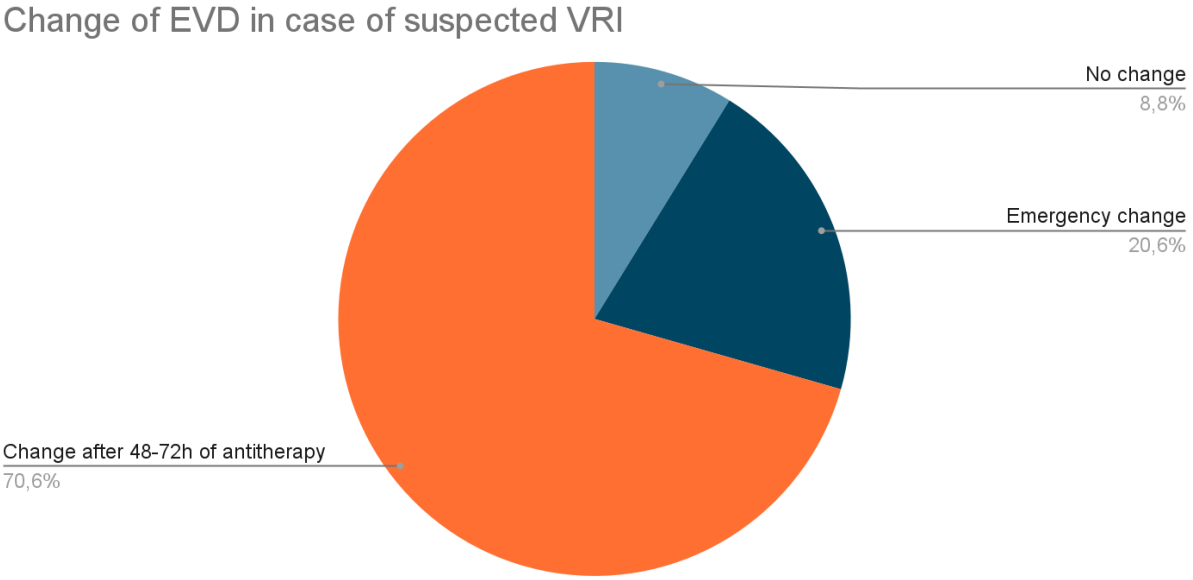
EVD tunneling



CSF sampling site

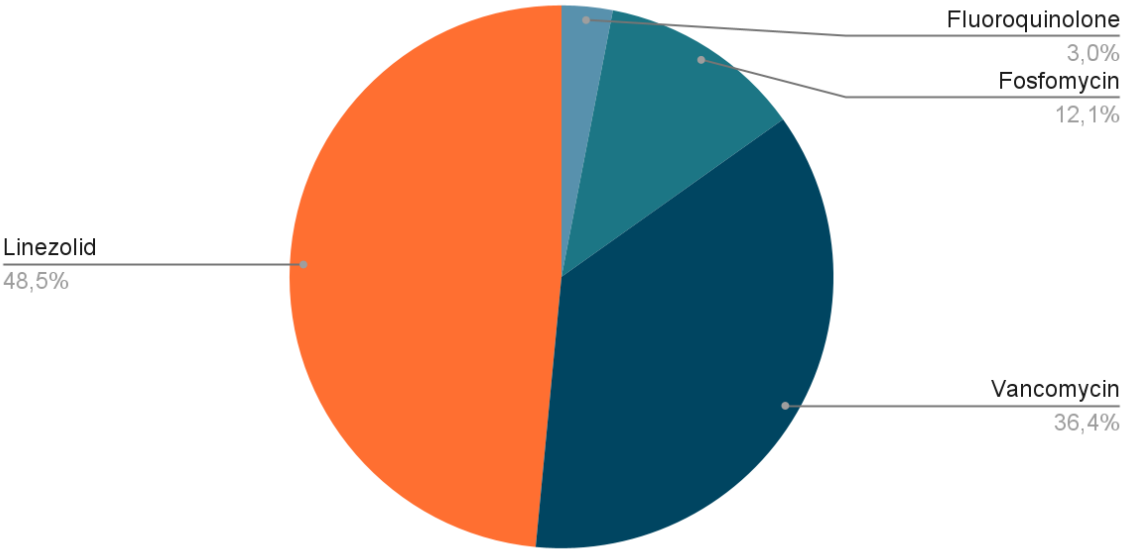



Brain imaging in case of suspected VRI
Never
5,9%
Always
26,5%
Sometimes
67,6%


Change of EVD in case of suspected VRI
No change
8,8%
Emergency change
20,6%
Change after 48-72h of antitherapy
70,6%

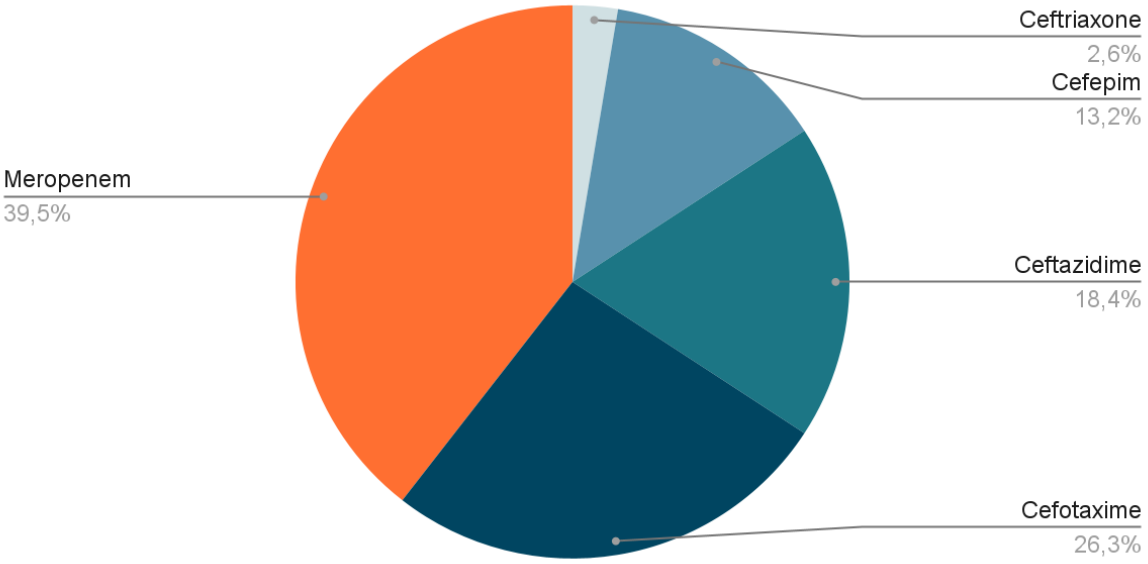
Empiric antibiotic therapy in case of suspected IRV

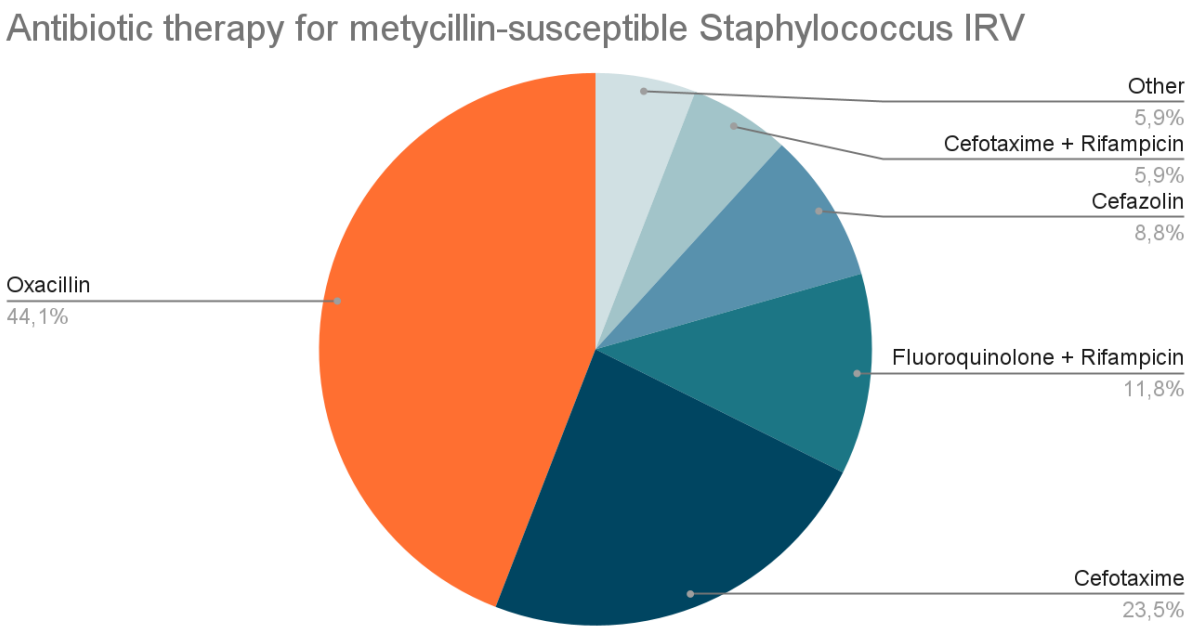
Anti-staphylococcal antibiotic

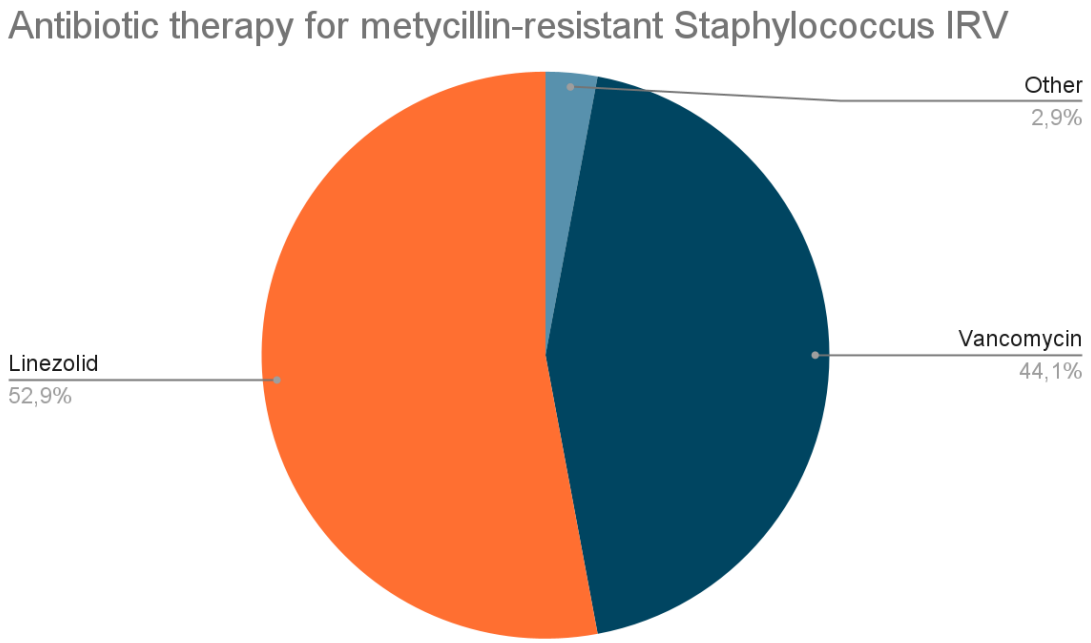


Empiric antibiotic therapy in case of suspected IRV

Anti gram negative bacteria antibiotics




Antibiotic therapy for metycillin-susceptible Staphylococcus IRV
Other
5,9%
Cefotaxime + Rifampicin
5,9%
Cefazolin
8,8%
Oxacillin
44,1%
Fluoroquinolone + Rifampicin
11,8%
Cefotaxime
23,5%

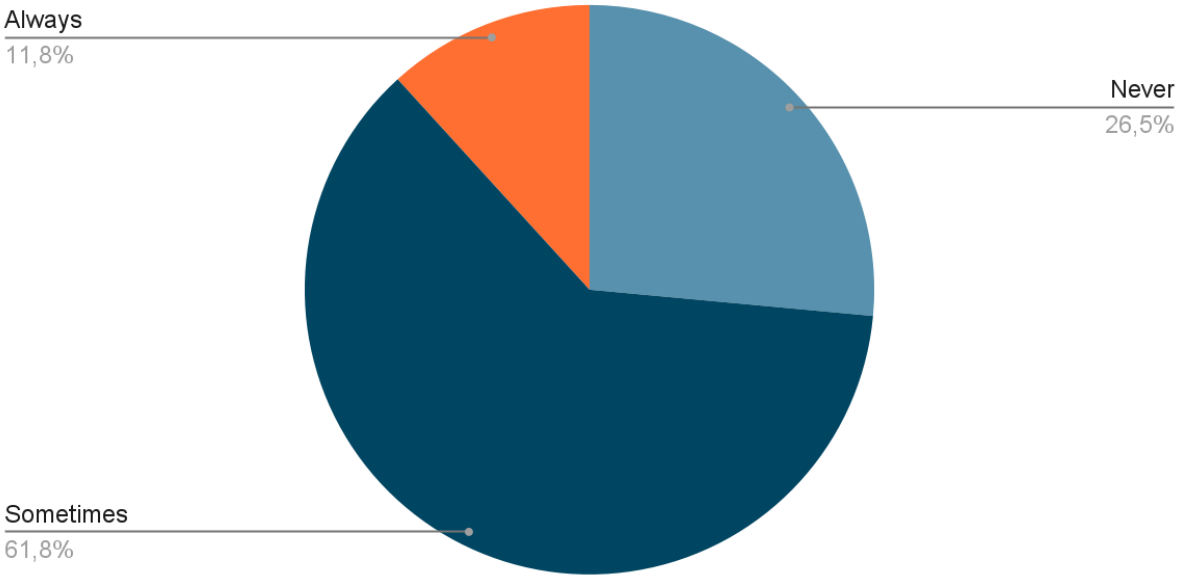

Antibiotic therapy for metycillin-resistant Staphylococcus IRV
Other
2,9%
Vancomycin
44,1%
Linezolid
52,9%

Duration of intravenous antibiotic therapy

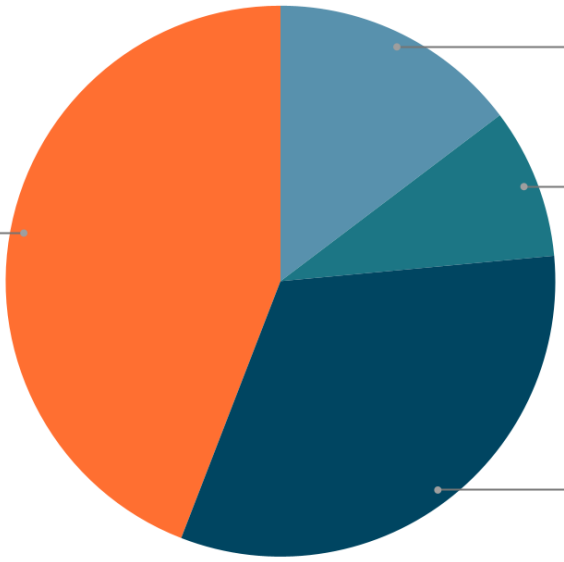
	7j	8-14j	15-21j	> 21j
Coag. neg. Staph.	15,2 %	63,6 %	21,2 %	0 %
Staph. Aureus	6,1 %	63,6 %	27,3 %	3,0 %
P. Acnes	12,9 %	51,6 %	25,8 %	9,7 %
P. Aeruginosa	0 %	39,4 %	45,5 %	15,2 %
Gram neg. bacteria	3,0 %	36,4 %	57,6 %	3,0 %

Antibiotic dosages in CSF

in case of intravenous antibiotic therapy

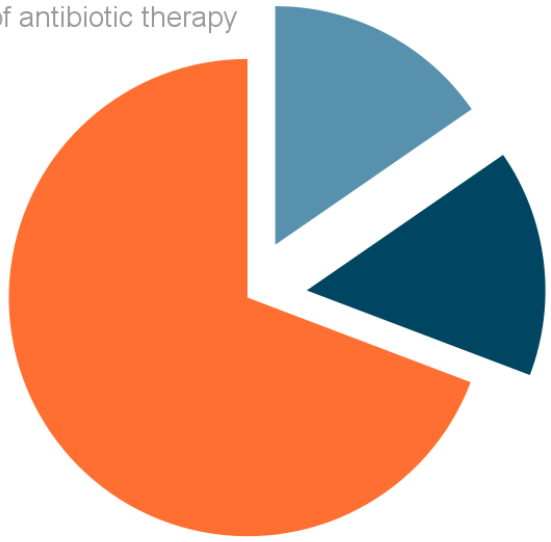


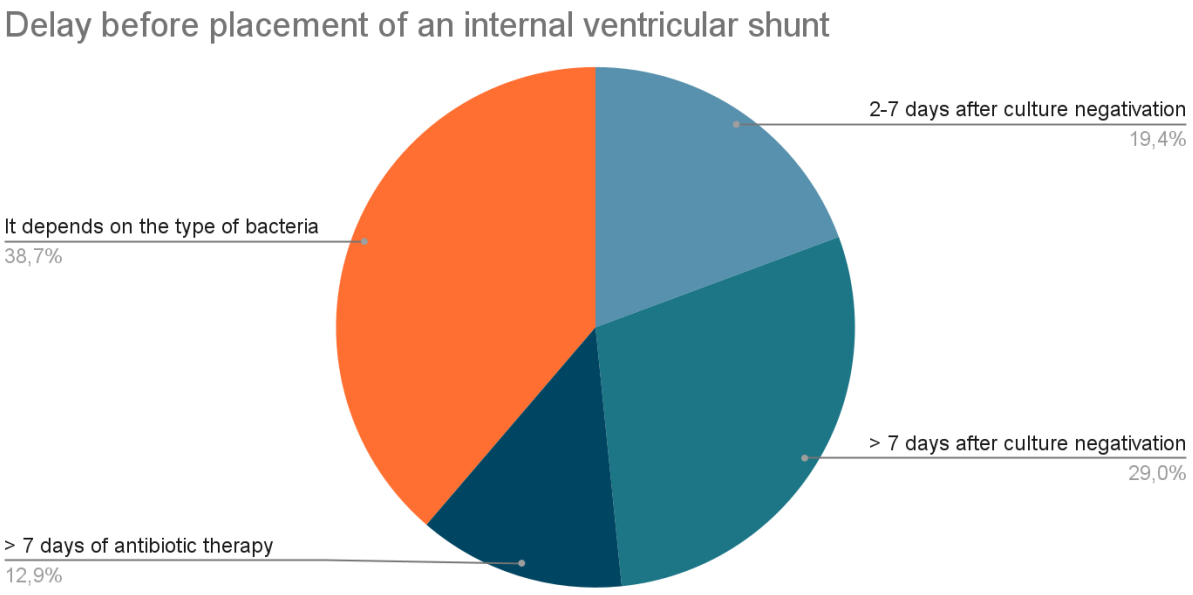
Evaluation of the efficacy of antibiotic therapy

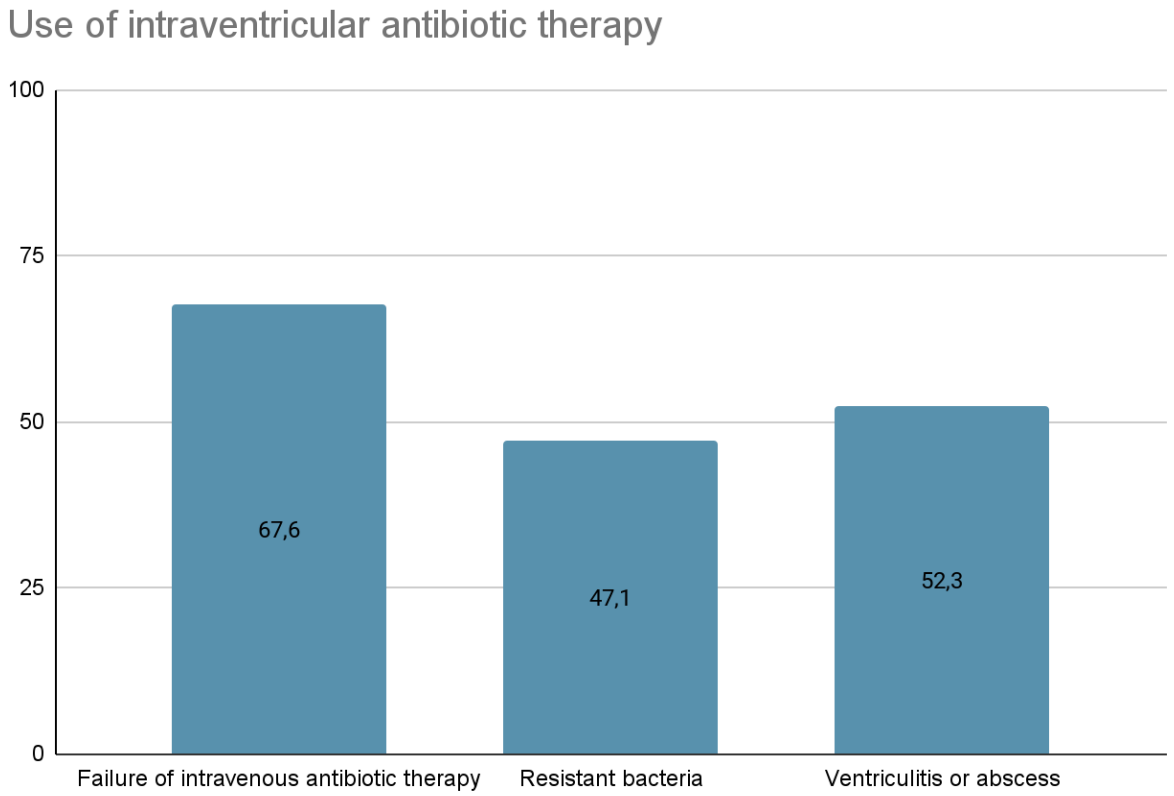


Analysis of the LCS

Evaluation of the efficacy of antibiotic therapy

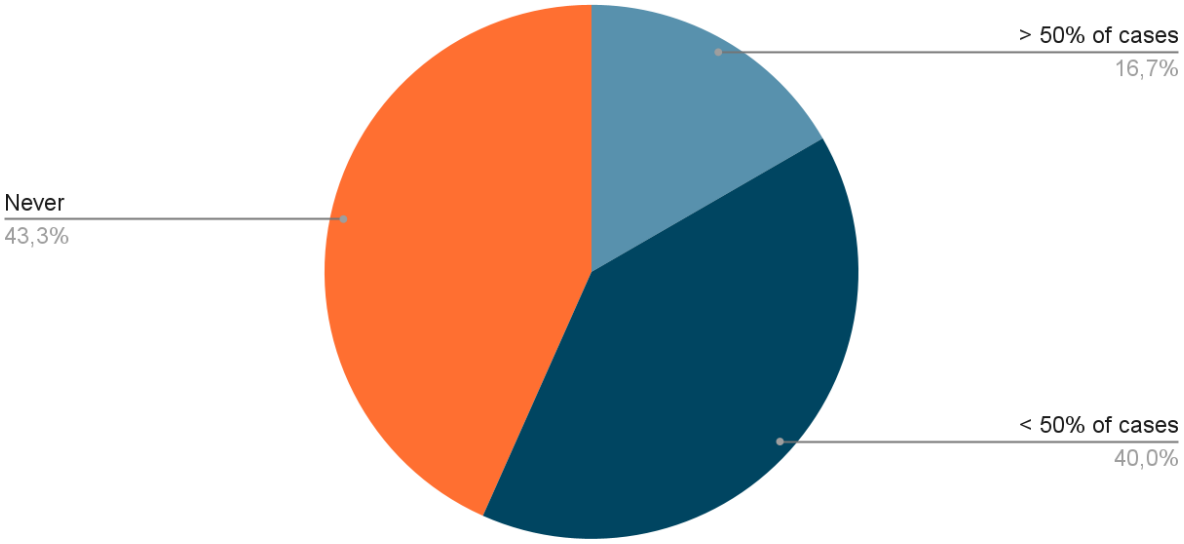



Delay before placement of an internal ventricular shunt
2-7 days after culture negativation
19,4%
It depends on the type of bacteria
38,7%
> 7 days after culture negativation
29,0%
> 7 days of antibiotic therapy
12,9%

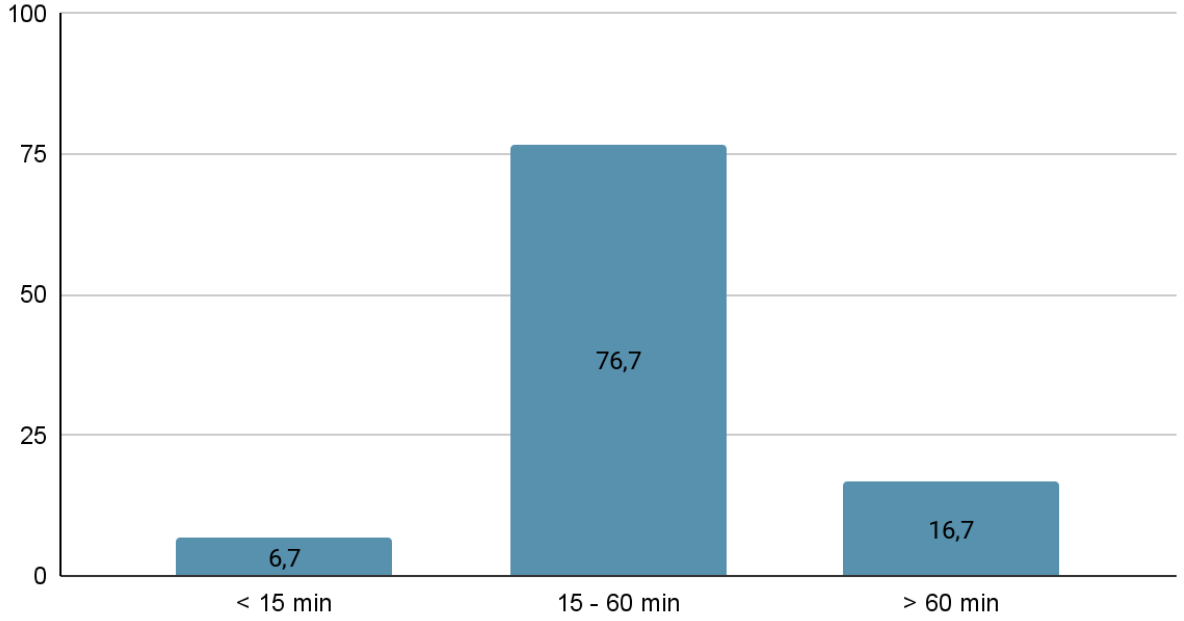

Use of intraventricular antibiotic therapy
100
75
50
25
0
67,6
47,1
52,3
Failure of intravenous antibiotic therapy
Resistant bacteria
Ventriculitis or abscess

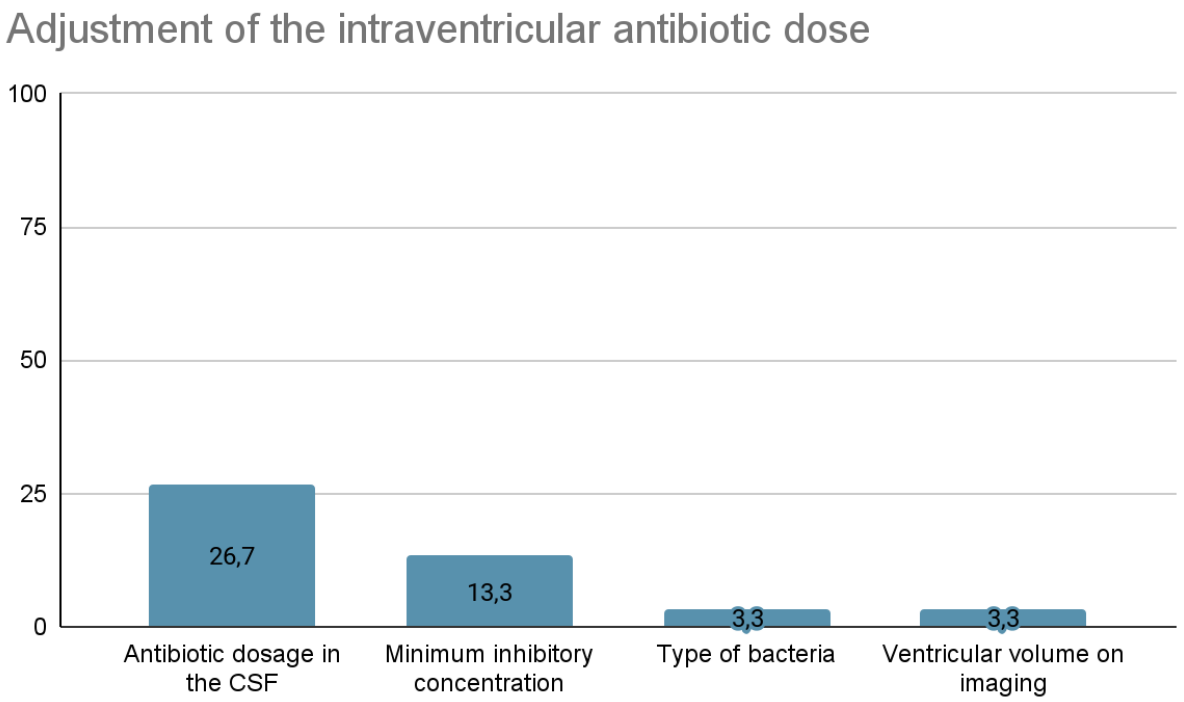
Antibiotic dosages in CSF

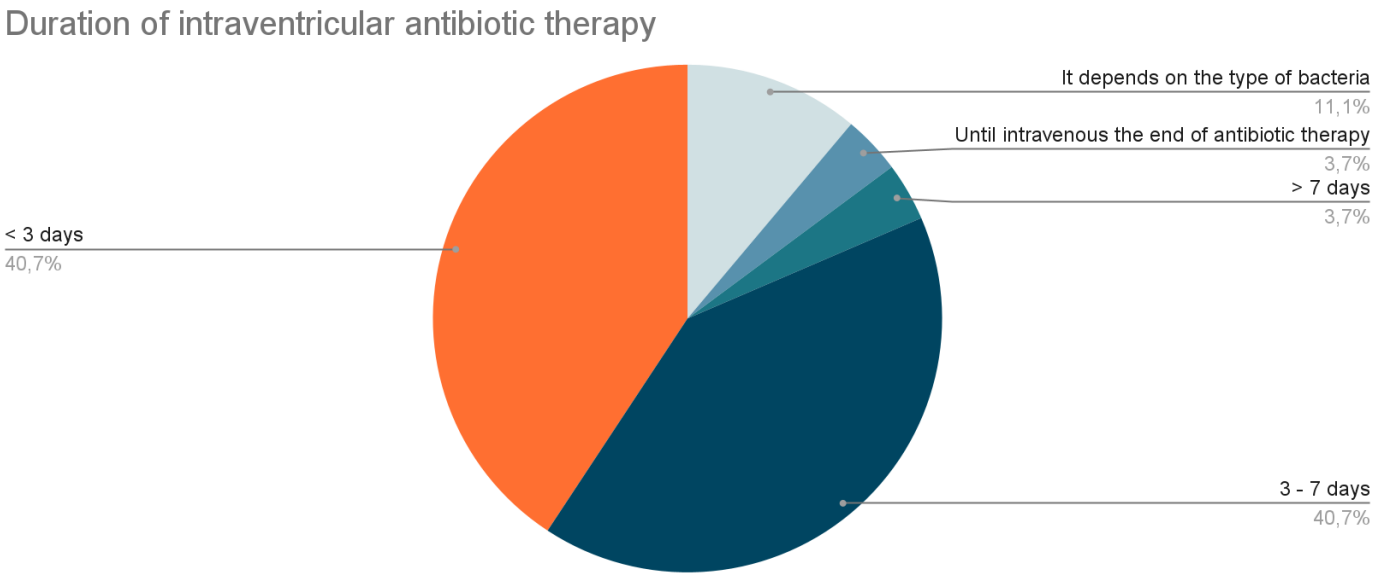
in case of intraventricular antibiotic therapy



EVD clamping time after intraventricular antibiotic injection




Adjustment of the intraventricular antibiotic dose
100
75
50
25
0
26,7
13,3
3,3
3,3
Antibiotic dosage in the CSF
Minimum inhibitory concentration
Type of bacteria
Ventricular volume on imaging


Duration of intraventricular antibiotic therapy
It depends on the type of bacteria
11,1%
Until intravenous the end of antibiotic therapy
3,7%
> 7 days
3,7%
< 3 days
40,7%
3 - 7 days
40,7%

Serment d’Hippocrate

En présence des Maîtres de cette école, de mes chers condisciples et devant l’effigie d’Hippocrate, je promets et je jure, au nom de l'Être suprême, d’être fidèle aux lois de l’honneur et de la probité dans l’exercice de la médecine.

Je donnerai mes soins gratuits à l’indigent et n’exigerai jamais un salaire au-dessus de mon travail.

Admis dans l’intérieur des maisons, mes yeux ne verront pas ce qui s’y passe, ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l’instruction que j’ai reçue de leurs pères.

Que les hommes m’accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert d’opprobre et méprisé de mes confrères si j’y manque.

Abstract

Introduction : Ventriculostomy related infections (VRI) are frequent, damaging and difficult to treat. The diagnostic methods and management of VRI are very heterogeneous, because evidence is lacking. The aim of our study is to evaluate the practices of neuro intensive care units in french-speaking European countries.

Materials and methods : This was a practice survey realized with an online questionnaire. The questionnaire included 30 items about 4 main topics (management of external ventricular drains (EVD), diagnosis of VRI, management of VRI, intraventricular antibiotic therapy). It was sent to intensive care units specialized in neurology and neurosurgery, in french-speaking European countries.

Results : The majority of centers (85,3 %) place their EVDs exclusively in the operating room, 61,8 % of the participants never use antibiotic prophylaxis during the placement and 79,4 % never use anti-infective impregnated EVD catheters. To help diagnose VRI, 38,2 % of participants use the cerebrospinal fluid (CSF) lactate assay, 17,6 % use the blood procalcitonin (PCT) assay, 67,6 % use the cell index, and 79,4 % sometimes use the 16S RNA PCR on the CSF. In case of suspected VRI, only 26,5 % of participants perform brain imaging systematically. For suspected VRI, the most common empiric antibiotic is Linezolid (48.5%) for Staphylococcus, and Meropenem (39.5%) for GNB. For documented methicillin-sensitive staphylococcus infections, the most prescribed antibiotic is Oxacillin (44.1%) ; for methicillin-resistant staphylococcus, the most frequent antibiotic is Linezolid (52.9%). Most participants (88.2%) sometimes use intraventricular antibiotic therapy, but never routinely. The majority of participants (76,5%) systematically perform CSF analysis to monitor the effectiveness of the treatment.

Conclusion : This study reveals that the management of ventriculostomy-related infections is highly heterogeneous between specialized centers in French-speaking Europe. This is due to the fact that the literature is not extensive on this subject, and current knowledge is mainly based on retrospective and small sample studies. It seems necessary to conduct randomized studies on this subject. European and French recommendations should help physicians to standardize their practices.

MeSH keywords : external ventricular drain, ventriculostomy-related infection, antibiotic, intraventricular, neuro intensive care unit

Résumé

Introduction : Les infections sur dérivations ventriculaires externes (DVE) sont fréquentes et graves. L'objectif de notre étude est d'évaluer les pratiques actuelles en neuro-réanimations.

Matériels et méthodes : Étude de pratiques professionnelles réalisée à l'aide d'un questionnaire sur 4 thèmes principaux (prise en charge des DVE, diagnostic des infections sur DVE, prise en charge des infections, antibiothérapie intraventriculaire).

Résultats : La plupart des participants (61,8 %) n'utilisent jamais d'antibioprophylaxie lors de la pose des DVE. Pour aider au diagnostic d'infection sur DVE, 38,2 % des participants utilisent le dosage du lactate dans le LCS, 17,6 % utilisent le dosage de la PCT dans le sang et 67,6 % utilisent l'index cellulaire. En cas de suspicion d'infection, seuls 26,5 % des participants réalisent systématiquement une imagerie cérébrale. En cas de suspicion d'infection sur DVE, l'antibiotique probabiliste le plus fréquemment utilisé est le Linézolide (48,5 %) pour les Staphylocoques, et le Méropénème (39,5 %) pour les bactéries gram négatif. La majorité des participants (88,2 %) utilisent parfois une antibiothérapie intraventriculaire, mais jamais de façon systématique.

Conclusion : La prise en charge des infections sur DVE est très hétérogène entre les centres spécialisés d'Europe francophone, ceci est dû au fait que la littérature est peu abondante sur ce sujet. Les recommandations européennes et françaises devraient aider les médecins à standardiser leurs pratiques.

Mots-clés MeSH : dérivation ventriculaire externe, antibiotique, intraventriculaire, réanimation